



Transdermal Drug Delivery For Chronic Pain & Management

¹Om A. Likhankar, ²Prof. Amruta S. Phuse; ³Dr. Nitin B. Kohale; ⁴Dr. Harigopal S. Sawarkar

¹Student of B. Pharm IIIrd Year

²Assistant Professor, Department of Pharmaceutics

³Professor, Department of Pharmaceutics

⁴Principal, Department of Pharmaceutical Chemistry

Dr. Rajendra Gode College of Pharmacy, Amravati – Maharashtra - 444604

Abstract: -

Pain management is a pressing problem that requires intricate mechanisms to be resolved. For localized acute pain, drugs must be administered quickly and precisely with little blood circulation diffusion, however for chronic pain, drugs must be released gradually with a lengthy half-life. A promising method with excellent patient compliance, the transdermal route was renowned for its painless delivery, lengthy drug retention period, steady blood concentration, easily adjustable dosage and release rate, and reduced side effects. This review explains the many analgesic mechanisms, dose forms, transdermal improvements, and clinical uses of transdermal pain treatment in accordance with the various sites of action that drugs seek to target. Here, we review progress and challenges in developing transdermal patches for sustained pain relief.

Keywords:

Pain management; Transdermal drug delivery; Analgesics; Sustained release; Chronic pain; Acute pain; Transdermal patches; Controlled drug release; Patient compliance; Targeted drug delivery; Pharmacokinetics; Clinical applications.

Introduction: -

TDDS has become one of the most widely investigated routes of noninvasive drug delivery into the body through the skin, unlike conventionally used direct administration routes that make use of needle-based injections. TDDS has significantly influenced the delivery of various therapeutic agents, especially in pain management, hormonal therapy, and treatment of diseases of the cardiovascular and central nervous systems (1).

SKIN:

The skin is the largest organ of the body and functions as a delivery site for a variety of drugs. Transdermal drug delivery systems offer multiple benefits compared to conventional delivery methods. They can provide both localized and systemic therapeutic effects. Some advantages of these systems include the ability to maintain controlled drug levels in the plasma, decrease the frequency of doses, and bypass hepatic first-pass metabolism. To achieve optimal effectiveness, it is essential to understand the kinetics, physical and chemical characteristics of the drug, as well as the route of drug transport. This manuscript concentrates on the principles of different physical methods to enhance transdermal drug delivery. The methods include iontophoresis, electrophoresis, photomechanical waves, ultrasound, needle-free injections, and microneedles. Various forms of energy, including mechanical, chemical, magnetic, and electrical, are utilized in these physical techniques. While oral delivery is effective for drugs that have high permeability in epithelial tissues and are soluble in water, it can be difficult to administer drugs that have low water solubility (2). The epidermis is made up of a keratinized stratified squamous epithelium and experiences a systematic process of proliferation, differentiation, and keratinization. The stratum corneum, which is the outermost layer of the epidermis, acts as the primary barrier between the body and external factors, with its lower region playing a vital role in blocking the entry of irritants and allergens. The thickness of the stratum corneum can differ based on the body region and the species (Monteiro-Riviere et al., 1990). Each cell within the stratum corneum, referred to as a corneocyte, measures 30 μm in diameter and 0.5–0.8 μm in thickness (Holbrook and Odland, 1974). These cells are neatly organized and layered upon one another, forming vertical interlocked columns with a flattened tetrakaidecahedron shape (Menten, 1976 a, b). This specific arrangement aids in sustaining the skin's effective barrier function. The lipids found within the stratum corneum originate from the lamellar granules (Odland bodies) in the stratum granulosum, contributing to the intercellular lipid component of the stratum corneum barrier. These lipids are structured into lamellar sheets that form the epidermal permeability barrier (3).

Your skin includes three layers known as;

- Dermis
- Epidermis
- Hypodermis

- **Dermis:** The dermis is a layer that measures between 3 to 5mm in thickness and is made up of a network of connective tissue, which includes blood vessels, lymphatic vessels, and nerve tissue. The blood supply in the skin is crucial for maintaining body temperature. Furthermore, it delivers nutrients and oxygen to the skin while also assisting in the removal of toxins and waste products. Capillaries extend up to 0.2mm from the skin's surface and create conditions that facilitate the penetration of most molecules through the skin barrier. Consequently, the circulation of blood keeps the concentration of a permeant in the dermis quite low, and this creates a concentration difference across the epidermis, which is necessary for transdermal permeation.

- **Epidermis:** The epidermis is the outermost, thin, and tough layer of the skin. Primarily, the cells found in the epidermis are known as keratinocytes; these cells originate in the innermost layer of skin, referred to as the basal layer. This layer functions as a barrier and is made up of dead cells, constituting the outermost section of the epidermis. It serves as an obstacle, as many drugs cannot penetrate the stratum corneum; however, lipotropic drugs can pass through more easily than hydrophilic drugs.

- **Hypodermis:** The hypodermis or subcutaneous fat tissue holds up the dermis and epidermis. It is described as a fat storage area. This layer helps to regulate temperature, provides nutritional support, and spontaneous protection. It carries the principal blood vessels and nerves to the skin and may contain sensory pressure organs. For transdermal drug delivery, the drug has to penetrate all the three layers and arriving in systemic circulation, figure. 1 (4).

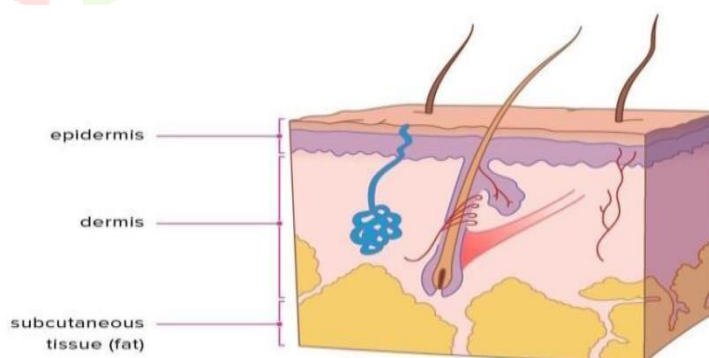


Figure 1: Structure of Skin

STRATUM CORNEUM:

The skin consists of multiple anatomically distinct layers. The stratum corneum primarily ensures the skin's protective function. This outer layer, which ranges from 10 to 20 mm in thickness, serves as the main barrier against the absorption of substances through the skin and prevents water loss. Beneath the stratum corneum lies the viable epidermis, measuring 50 to 100 mm thick, which is responsible for producing the stratum corneum. The dermis, which is 1 to 2 mm thick, is situated directly below the epidermis and provides structural support to the skin (5).

The stratum corneum is the top layer of the epidermis and represents the final phase of keratinocyte maturation and development. Keratinocytes located in the basal layer of the epidermis are capable of proliferation, and as these cells mature toward the surface, they gradually lose their ability to divide and undergo programmed cell death. These fully matured, enucleated keratinocytes are referred to as corneocytes, which contain only keratin filaments that are embedded in a filaggrin matrix. The plasma membranes of the prior keratinocytes are replaced by cornified lipid envelopes, and the cells become flattened, forming connections with one another via corneodesmosomes, thereby stacking in layers to create the stratum corneum (6).

The human stratum corneum consists of approximately 15 layers of flattened corneocytes and is categorized into two layers: the stratum compactum and the stratum disjunctum. The stratum compactum is the lower, denser layer that is cohesive, while the stratum disjunctum is the upper, more loosely arranged layer located above the stratum compactum. As the stratum disjunctum progressively loses its adhesion due to reduced inter-corneocyte connections, the cells shed (7).

TRANSDERMAL DRUG DELIVERY SYSTEM [TDDS]:

Transdermal drug delivery systems (TDDS) are designed to provide the correct medicinal dosage through the skin of a patient, allowing for the therapeutic drug to enter the body. To ensure systemic effects by delivering therapeutic agents through the human skin, it's crucial to thoroughly consider the skin's biophysical, morphological, and physicochemical characteristics. Transdermal drug delivery offers significant benefits over injectable and oral methods, as it enhances patient adherence and bypasses first-pass metabolism (8).

A transdermal patch is a specialized medicated adhesive patch that is designed to deliver drugs into the bloodstream at a steady rate through the skin's layers. These patches provide a very convenient way to administer drug, as they are painless and can offer ongoing treatment for several days. Furthermore, they can be easily removed at any moment. Transdermal patches are available in different sizes and can contain various active ingredients. Upon application to the skin, these patches employ diffusion processes to transfer these active ingredients directly into the bloodstream. Certain patches may have high concentrations of the

active ingredient, which remains on the skin for a prolonged duration. Nitroglycerin was the first transdermal patch created in 1985, representing a major advancement in this method of drug delivery. A range of drugs is developed as transdermal patches, including nicotine, estradiol, fentanyl, clonidine, scopolamine (hyoscine), and estradiol with norethisterone acetate. The specific location for applying the patch is determined by the type of drug therapy being used (9).

TRANSDERMAL PATCHES:

A transdermal patch is a medical adhesive that can release drug directly into the bloodstream through the skin layers at a specified rate. In fact, these patches offer the most convenient method of drug delivery. They are non-invasive, can provide treatment over several days, and can be removed anytime. Available in various sizes, they contain multiple active ingredients. When placed on the skin, the patch facilitates the release of active compounds into the bloodstream through diffusion processes. Transdermal patches may include substantial amounts of active substances that can stay on the skin for prolonged durations. The nitroglycerine patch, developed in 1985, was one of the first transdermal patches created. The transdermal drug delivery system offers several benefits compared to other administration methods. These advantages include the capability to provide continuous drug doses over extended periods, the ability to bypass the gastrointestinal tract, and the avoidance of first-pass metabolism in the liver figure. 2 (10).

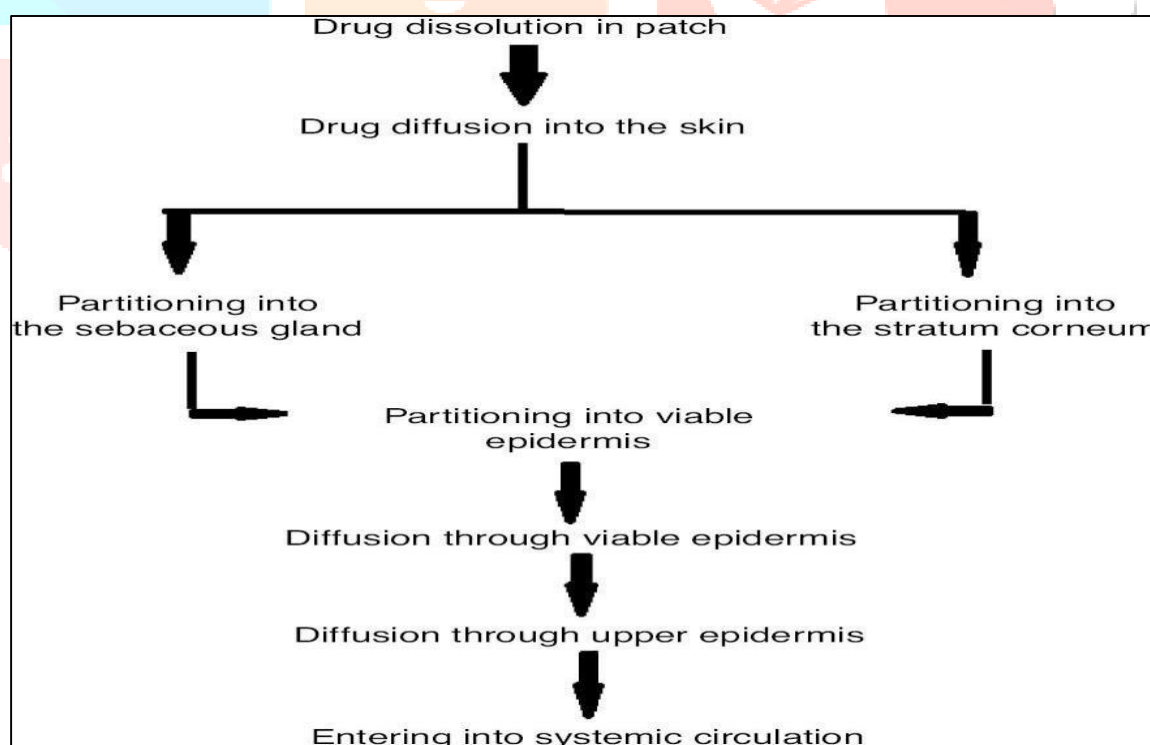


Figure 2: Drug Dissolution in Transdermal patch

BASIC COMPONENTS OF TRANSDERMAL PATCH:

Transdermal patches are typically made up of multiple layers designed to deliver drug through the skin and into the bloodstream. These layers illustrate the fundamental components of a medicated patch. The exact formulation and structure of the patch may differ based on the drug being administered and the intended rate of drug delivery. The outermost layer, known as the backing layer, protects the other layers from external elements. This layer is commonly constructed from a flexible and waterproof material like polyethylene or polypropylene. The adhesive layer is responsible for securing the patch to the skin, ensuring it remains in place. It is generally made with a durable, hypoallergenic adhesive that is gentle on the skin. The drug layer contains the drugs intended for transdermal delivery and is designed to release the drugs steadily over time. The rate-controlling membrane regulates the pace at which the drugs are released from the patch (11).

TYPES OF TRANSDERMAL PATCHES:

In general, there are four main type of transdermal medical patches;

- Drug -in adhesive
- Reservoir
- Matrix
- Micro-reservoir

○ **Drug-in adhesive system:** This is the most basic type of membrane permeation control system. The adhesive layer in this system holds the drugs and acts as a bond between the various layers. The drug mixture is placed between the liner and the backing.

○ **Reservoir system:** In this configuration, the drug reservoir is situated between the backing layer and the membrane that controls the release rate, with the drug being emitted through the porous membrane. The drug may exist in various forms, including solution, suspension, or gel, or it can be integrated within a solid polymer matrix inside the reservoir compartment.

○ **Matrix system:** In this approach, drugs are evenly distributed within either hydrophilic or lipophilic polymer matrices. The resulting polymer that contains the drug is attached to discs with controlled thickness and surface area.

○ **Micro-reservoir:** This system merges aspects of both the reservoir and matrix dispersion systems. In this case, drug particles are initially suspended in an aqueous solution of a water-soluble liquid polymer, and this solution is then uniformly dispersed within a lipophilic polymer to form thousands of minute, non-leaching drug reservoirs figure 3

(12).

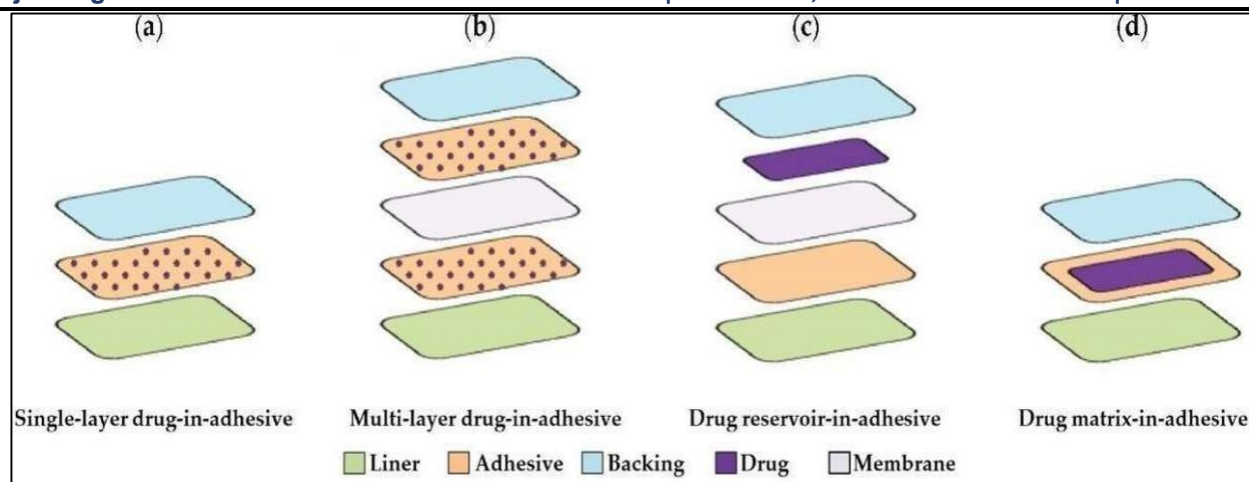


Figure 3: Types of Transdermal Patches

ADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEM:

- ✓ It replaces oral administration when it is not appropriate, such as when vomiting or diarrhoea occurs.
- ✓ It avoids parenteral therapy's hazards and drawbacks.
- ✓ It prevents the "first pass" effect in the liver.
- ✓ It prevents gastrointestinal absorption fluctuations caused by changes in pH, enzyme activity, drug-food interactions, and other factors.
- ✓ It increases therapeutic efficacy and decreases adverse effects as a result of improving the blood concentration-time profile and preventing drug from entering the bloodstream by pulse entry (13).

DISADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEM:

- ✓ Drug that requires high blood levels cannot be given; only strong compounds, 10 mg or less per day, are allowed.
- ✓ Transdermal administration is often intended to provide slow, sustained drug delivery; it is not a method for achieving quick bolus-type drug input.
- ✓ Another significant drawback is dermatitis, or skin irritation, brought on by enhancers and excipients in drug delivery systems that increase percutaneous absorption (14).

TRANSDERMAL PATCHES USED AS ANTI-INFLAMMATORY AGENT (NSAID):

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently utilized to alleviate pain and inflammation in both humans and various animal species, proving particularly beneficial for managing chronic inflammatory disorders. NSAIDs are often prescribed for relief after dental extractions. Besides their prolonged effect and high absorption rates, transdermal NSAIDs provide several additional advantages. One critical aspect of drug administration is the delivery method, and transdermal patches are as effective as taking drugs orally. Several analgesics, including diclofenac and ketoprofen, can be delivered through patches. Research has been conducted to compare the efficacy of diclofenac and ketoprofen, assessing how

well transdermal patches perform in relation to oral drugs. Furthermore, studies have evaluated the effectiveness of both diclofenac and ketoprofen when given orally versus transdermally. As an alternative to oral administration, this method may improve patient acceptance by reducing adverse reactions (15). Additionally, it eliminates the discomfort associated with intramuscular (IM) and intravenous (IV) routes of administration. This category of topically applied NSAIDs can be administered systemically in low doses. The transdermal application of the drug may diminish its effectiveness and the subsequent side effects commonly associated with oral intake (16).

THE DEVELOPMENT OF PATCHES FOR SUSTAINED PAIN RELIEF:

Transdermal patches offer an effective method for delivering drug directly through the skin, ensuring consistent and controlled drug release for dependable therapeutic outcomes. The importance of this delivery system could be enhanced if advancements in technology lead to the development of transdermal patches capable of administering exact dosages based on live data or monitoring vital signs. For patients with delicate stomachs or those who experience nausea from drugs, transdermal drug delivery systems (TDDSs) present the advantage of avoiding frequent injections or oral pill consumption (17). TDDSs, which provide a continuous supply of pain relief, can assist individuals facing chronic pain and difficulties with swallowing. By decreasing the likelihood of missed doses, this non-invasive method of drug delivery improves drug adherence and eliminates the need for recurrent injections or invasive techniques. The benefits of TDDSs compared to traditional oral and intravenous treatments for chronic pain management are significant, emphasizing the importance of appropriate dosage delivery and monitoring for side effects. TDDSs provide a convenient and effective means of administering drugs (18).

THE DIFFICULTIES IN PATCHES FOR SUSTAINED PAIN RELIEF:

With transdermal drug delivery systems, drugs are administered through the skin and subsequently enter the bloodstream, allowing them to circulate throughout the body. Both hydrophilic and hydrophobic drugs can utilize this method. Inflammation manifests through symptoms such as redness, swelling, pain, heat, and loss of function. This condition is the body's response to harmful stimuli, disease, or injury. Various chemical mediators, including histamine, complement proteins, kinins, eicosanoids, and monokines, play a role in regulating this process. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly employed to manage conditions like osteoarthritis, soft-tissue injuries, and fractures due to their effectiveness in alleviating postoperative pain (19).

Reviews also consider scientific and technological challenges, such as the skin's barrier properties and formulation issues, which contribute to overcoming limitations and improving system effectiveness (20).

NSAID PATCHES:

NSAIDs can increase the risk of heart attack, stroke, and bleeding in the stomach or elsewhere in the gastrointestinal tract. Seek medical attention if you have:

- Shortness of breath
- Slurred speech
- Nausea
- Weakness
- Diarrhoea
- Yellow skin or eyes
- Indigestion
- Stomach pain
- Vomiting blood
- Swelling
- Blood in your bowel movement

Conclusion:

The transdermal route of drug delivery is seen to be both safe and efficacious in comparison to other ways of administration. Many pharmaceuticals are designed in Transdermal Drug Delivery Systems (TDDS) to reduce gastrointestinal side effects and first-pass metabolism, such as hormone treatments, a wide range of analgesics, and heart disease drugs. As transdermal drug delivery systems gain popularity and offer numerous benefits, researchers are concentrating more on developing novel drugs in this administration method. Although the skin has many benefits, it is important to recognize that its primary role is to protect interior organs. The goal of developing a transdermal medicine delivery system is to reduce the amount of disruption to the skin's normal processes. Drug delivery via the transdermal method may affect skin physiology, which emphasizes how crucial it is to minimize such changes. To advance in this subject, a thorough understanding of skin anatomy and physiology is necessary.

References:

1. Roohnikan, M., Laszlo, E., Babity, S., & Brambilla, D. (2019). A snapshot of transdermal and topical drug delivery research in Canada. *Pharmaceutics*, 11(6), 256. <https://doi.org/10.3390/pharmaceutics11060256>
2. Sharma, M., Sharma, R., & Jain, D. K. (2016). Nanotechnology-based approaches for enhancing oral bioavailability of poorly water-soluble antihypertensive drugs. *Scientifica (Cairo)*, 2016, 8525679. <https://doi.org/10.1155/2016/8525679>
3. Monteiro-Riviere, N. A., & Larese Filon, F. (2017). *Adverse effects of engineered nanomaterials* (2nd ed.). Elsevier.
4. Singh, D., et al. (2022). Recent advances of transdermal drug delivery systems. *Journal of Pharmaceutical Negative Results*, 13, 4452–4459.
5. Bouwstra, J. A., Honeywell-Nguyen, P. L., Gooris, G. S., & Poncet, M. (2003). Progress in lipid research. *Progress in Lipid Research*, 42(1), 1–36.
6. Kim, J. H., Ahn, B., Choi, S. G., In, S., Goh, A. R., Park, S. G., Lee, C. K., & Kang, N. G. (2019). Amino acids disrupt calcium-dependent adhesion of stratum corneum. *PLoS ONE*, 14(4), e0215244. <https://doi.org/10.1371/journal.pone.0215244>
7. Arriagada, F., & Morales, J. (2019). Limitations and opportunities in topical drug delivery: Interaction between silica nanoparticles and skin barrier. *Current Pharmaceutical Design*, 25(4), 455–466. <https://pubmed.ncbi.nlm.nih.gov/30663527>
8. Allen, L. V., Popovich, N. G., & Ansel, H. C. (2005). *Pharmaceutical dosage forms and drug delivery systems* (8th ed.). Wolters Kluwer Publishers.
9. Kumar, P., Sankar, C., & Mishra, B. (2004). Delivery of macromolecules through skin. *Indian Pharmacist*, 5(37), 17.
10. Berner, B., & John, V. A. (1994). Pharmacokinetic characterisation of transdermal delivery systems. *Clinical Pharmacokinetics*, 26(2), 121–134. <https://doi.org/10.2165/00003088-199426020-00005>
11. Youngkin, E. Q. (1990). Estrogen replacement therapy and the estraderm transdermal system. *Nurse Practitioner*, 15(5), 19–26, 31. <https://doi.org/10.1097/00006205-199005000-00005>
12. Wokovich, A. M., Prodduturi, S., Doub, W. H., Hussain, A. S., & Buhse, L. F. (2006). Transdermal drug delivery system (TDDS) adhesion as a critical safety, efficacy and quality attribute. *European Journal of Pharmaceutics and Biopharmaceutics*, 64(1), 1–8. <https://doi.org/10.1016/j.ejpb.2006.03.009>
13. Bhowmik, D., Duraivel, S., & Kumar, K. P. (2012). Recent trends in challenges and opportunities in transdermal drug delivery system. *The Pharma Innovation Journal*, 1(9), 23–29.
14. Kaware, A., Waghmare, S., & Kamble, H. (2022). Recent advances in transdermal drug delivery systems: A review. *Biomaterials Research*, 26, 85762. <https://doi.org/10.1186/s40824-022-00293-7>

15. Shankar, D., Sinha, A., Anand, S., Verma, N., & Choudhary, S. (2021). Efficacy of transdermal diclofenac patch and ketoprofen patch as postoperative analgesia after extraction of first premolars bilaterally in both arches for orthodontic purpose: A comparative study. *Journal of Pharmacy and Bioallied Sciences*, 13, 0–4. https://doi.org/10.4103/jpbs.JPBS_571_20
16. Ghlichloo, I., & Gerriets, V. (2022). *Nonsteroidal anti-inflammatory drugs (NSAIDs)*. StatPearls Publishing.
17. Tiwari, C., Choudhary, M., Malik, P., Jaiswal, P. K., & Chauhan, R. (2022). Transdermal patch: A novel approach for transdermal drug delivery. *Journal of Drug Delivery and Therapeutics*, 12, 179–188.
18. Higo, N. (2007). The recent trend of transdermal drug delivery system development. *ChemInform*, 38, 655–662. <https://doi.org/10.1002/chin.200732279>
19. Vikrant, A., & Arya, M. L. (2011). A review on anti-inflammatory plant barks. *International Journal of PharmTech Research*, 3(2), 899–908.
20. Prausnitz, M. R., & Langer, R. (2008). Transdermal drug delivery. *Nature Biotechnology*, 26(11), 1261–1268. <https://doi.org/10.1038/nbt.1504>

