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"A REVIEW ON TRANSDERMAL DRUG DELIVERY OF NSAIDS: MECHANISTIC INSIGHTS AND FORMULATION STRATEGIES"

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ABSTRACT

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are among the most commonly used therapeutic agents for managing pain, inflammation, and fever. However, conventional oral administration is often limited by gastrointestinal irritation, hepatic toxicity, and renal complications due to systemic exposure and first-pass metabolism. To overcome these drawbacks, transdermal drug delivery systems (TDDS) have gained significant attention as an effective and non-invasive alternative route of administration. The transdermal route offers sustained and controlled drug release, bypasses hepatic first-pass metabolism, minimizes gastrointestinal side effects, and enhances patient compliance. Successful transdermal delivery depends on several physicochemical and biological factors, including drug lipophilicity, molecular weight, and skin permeability. Various formulation strategies such as vesicular systems, nanocarriers, microemulsions, and hydrogels have been developed to enhance the penetration and bioavailability of NSAIDs through the skin. Despite promising advancements, challenges like limited permeability, formulation stability, and scalability remain. Overall, transdermal delivery of NSAIDs presents a promising approach for achieving effective, sustained, and safe therapeutic outcomes in chronic pain and inflammatory conditions.

KEYWORDS: NSAIDs, Transdermal drug delivery, COX inhibition, Nanocarriers, Permeation enhancement, Sustained release.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) represent one of the most widely used classes of therapeutic agents for the treatment of pain, inflammation, and fever. They exert their pharmacological effects primarily through the inhibition of cyclooxygenase (COX) enzymes COX-1 and COX-2 thereby suppressing the synthesis of prostaglandins, which are key mediators of inflammation and pain.[1,2] Despite their efficacy, conventional oral administration of NSAIDs is often associated with significant gastrointestinal (GI) irritation, ulceration, renal toxicity, and hepatic dysfunction due to systemic exposure and first-pass metabolism.[1,4] These adverse effects have prompted growing interest in developing alternative routes of administration that can improve therapeutic outcomes and patient compliance.

Among these, the transdermal route has emerged as a promising non-invasive alternative that offers sustained and controlled drug release, avoidance of GI side effects, and improved bioavailability.[3] Transdermal drug delivery systems (TDDS) provide a steady-state plasma concentration, enhance patient compliance through reduced dosing frequency, and bypass hepatic first-pass metabolism.[4] Such advantages make transdermal delivery particularly attractive for chronic pain management using NSAIDs such as diclofenac, ketoprofen, and ibuprofen.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

One of the most popular medicine classes for treating pain, inflammation, and fever is non-steroidal anti-inflammatory drugs, or NSAIDs. Cyclooxygenase (COX) enzymes are important mediators in the manufacture of prostaglandins and thromboxanes from arachidonic acid, and their inhibition is the main way they produce their therapeutic effects. Inhibiting prostaglandins has analgesic, anti-inflammatory, and antipyretic effects since they are essential for causing inflammation, activating pain receptors, and causing fever.[1] Based on their selectivity, NSAIDs can be broadly divided into two groups: non-selective COX inhibitors, which inhibit both COX-1 and COX-2 isoenzymes, like ibuprofen, diclofenac, naproxen, indomethacin, and ketoprofen, and selective COX-2 inhibitors, which preferentially inhibit the inflammatory inducible COX-2 enzyme while preserving the

constitutive COX-1 enzyme that protects the stomach mucosa and prevents platelet aggregation.[2,3]

Rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, gout, musculoskeletal pain, dysmenorrhea, and postoperative pain are only a few of the acute and chronic inflammatory diseases for which NSAIDs are used therapeutically.[3] Because of their quick start of action and efficiency in lowering pain and swelling, they are frequently utilised as first-line agents.[4] Owing mainly to COX-1 inhibition and local acidic irritation of the gastric mucosa, oral NSAID therapy is often linked to gastrointestinal (GI) problems as irritation, ulceration, bleeding, and perforation, even though they are effective.[3,4] Additionally, prolonged use might result in hepatotoxicity, cardiovascular hazards, and renal impairment, especially in older people or those with underlying medical issues.

Mechanism of Action of NSAIDs

The main pharmacological mechanism by which non-steroidal anti-inflammatory drugs (NSAIDs) work is by preventing the cyclooxygenase (COX) enzymes from converting arachidonic acid into prostaglandins and thromboxanes.[6] The substrate for the COX pathway is arachidonic acid, a polyunsaturated fatty acid that is liberated from membrane phospholipids by phospholipase A_2 . Cyclooxygenase comes in two primary isoforms, COX-1 and COX-2, each of which has a different physiological function and tissue distribution.[7]

A constitutive enzyme found in most tissues, COX-1 is essential for preserving regular physiological processes such the preservation of the stomach mucosa, control of renal blood flow, and platelet aggregation by generating prostaglandins and thromboxane A_2 . On the other hand, COX-2 is an inducible enzyme that is mostly expressed at inflammatory areas in reaction to endotoxins, growth factors, and cytokines. The inflammatory response is characterised by vasodilation, increased vascular permeability, and pain receptor sensitisation, all of which are facilitated by the prostaglandins generated by COX-2.[8]

NSAIDs reduce the production of prostaglandins (PGs) and thromboxanes (TXs) by inhibiting both COX isoforms to differing degrees. Because prostaglandins are important mediators of inflammatory processes, its inhibition reduces inflammation. While the antipyretic effect results from the inhibition of prostaglandin E_2 (PGE_2) synthesis in the hypothalamus, which normalises the elevated body temperature during fever, the analgesic

effect is caused by the decreased sensitivity of nociceptors (pain receptors) to chemical and mechanical stimuli.[6,8]

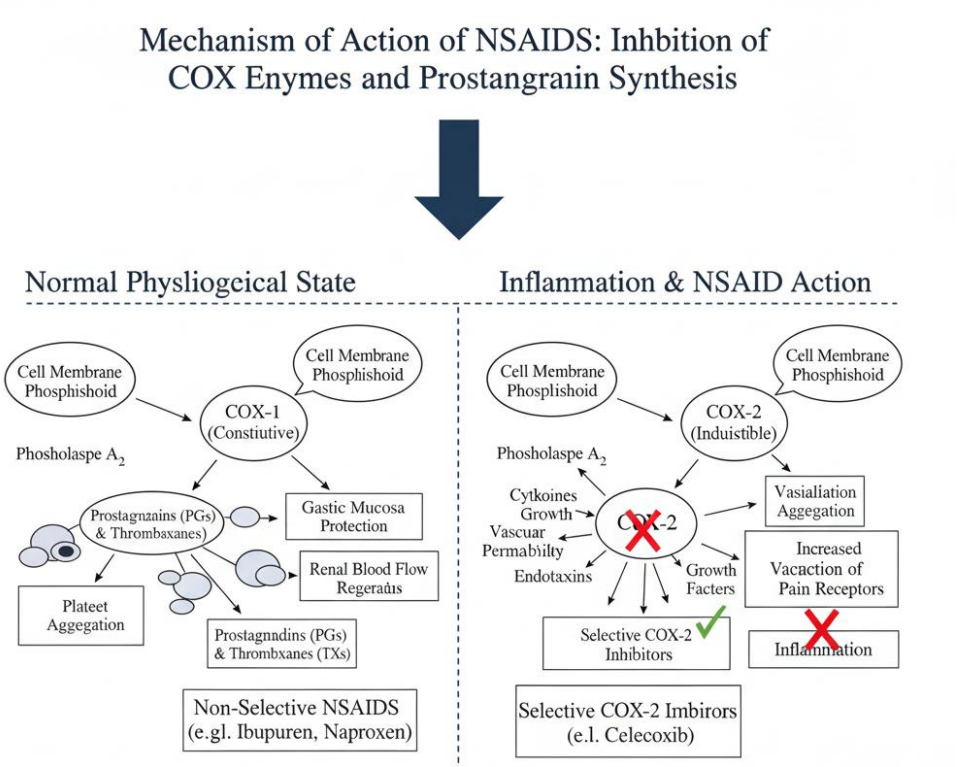

Figure 1: Mechanism of NSAIDs Drugs.

Inhibiting both COX-1 and COX-2, non-selective NSAIDs like ibuprofen, diclofenac, and naproxen have good anti-inflammatory and analgesic benefits but also cause side effects including ulceration and gastrointestinal irritation because they lower the stomach's protective prostaglandins. To get around these restrictions, selective COX-2 inhibitors (such celecoxib and etoricoxib) were created to minimise gastrointestinal adverse effects by targeting the inflammatory COX-2 isoform while leaving COX-1 unaltered.

Need for Alternative Routes of Administration of NSAIDs[9-11]

- Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are widely prescribed for managing pain, inflammation, and fever.
- Conventional oral administration of NSAIDs has several limitations, prompting the search for alternative delivery systems.
- Oral NSAIDs undergo extensive first-pass metabolism in the liver, reducing their bioavailability and therapeutic efficacy.

- Prolonged oral use can cause gastrointestinal (GI) complications such as irritation, ulceration, bleeding, and perforation.
- GI complications arise due to inhibition of COX-1–mediated protective prostaglandin synthesis in the gastric mucosa.
- These adverse effects are especially concerning for patients requiring long-term NSAID therapy for chronic conditions like rheumatoid arthritis or osteoarthritis.
- Oral administration can cause fluctuations in plasma drug concentration, leading to subtherapeutic effects or toxicity.
- Frequent dosing is often needed to maintain effective drug levels, resulting in poor patient compliance.
- Patients with hepatic or renal impairment may experience worsened organ function due to systemic exposure and metabolic burden.
- Oral therapy may be inconvenient or intolerable for patients experiencing nausea, vomiting, or difficulty swallowing tablets.
- Parenteral routes (intramuscular or intravenous) provide rapid onset but are invasive, painful, and unsuitable for chronic use.
- Rectal and sublingual routes have limitations like inconsistent absorption, local irritation, and patient discomfort.
- These challenges highlight the need for alternative, patient-friendly drug delivery systems.
- Transdermal drug delivery systems (TDDS) have gained attention as an emerging alternative.
- The transdermal route allows direct absorption into systemic circulation, bypassing hepatic first-pass metabolism.
- TDDS reduces gastrointestinal toxicity and provides a steady plasma drug concentration.

Advantages of the Transdermal Route for NSAID Delivery[12-15]

- The transdermal route provides sustained and controlled drug release, maintaining steady plasma levels and reducing dosing frequency.
- It bypasses gastrointestinal irritation and prevents gastric ulcers, bleeding, and discomfort associated with oral NSAIDs.
- The route avoids first-pass hepatic metabolism, improving bioavailability and reducing systemic toxicity.

- Transdermal systems are non-invasive, convenient, and enhance patient compliance due to easy application and removal.
- They enable both localized and systemic delivery, achieving targeted therapeutic effects with minimal side effects.

Transdermal Patch

An innovative, non-invasive drug delivery method called a transdermal patch is intended to administer a precise dosage of medication via the skin and into the bloodstream over an extended length of time.[16] It provides regulated and prolonged medication release with better patient compliance, making it a practical substitute for oral and parenteral administration. Although the human skin, especially the stratum corneum, serves as a natural barrier against outside substances, medications can be efficiently administered through the skin in therapeutic concentrations with the use of specific formulation techniques.[16] For medications like hormones, cardiovascular agents, analgesics, and non-steroidal anti-inflammatory medicines (NSAIDs), where stable plasma levels and the avoidance of gastrointestinal adverse effects are preferred, transdermal patches have drawn a lot of interest.[17]

The fundamental idea behind a transdermal patch is that the medication diffuses into the systemic circulation from the patch through the stratum corneum, the epidermis, and dermis. Fick's law of diffusion governs this process, which involves the medication moving from a patch, which has a greater concentration, to the skin, which has a lower concentration. The physicochemical characteristics of the drug (molecular weight, lipophilicity, and solubility), the kind of formulation, and the state of the skin all affect how quickly the drug is absorbed. Low molecular weight (<500 Da), balanced lipophilicity (log P between 1 and 4), and strong activity at low dosages are usually characteristics of the best medications for transdermal delivery.[15,17,18]

A transdermal patch generally consists of several layers, each serving a specific function

- Backing layer: It provides physical protection and mechanical strength to the patch while preventing drug loss and environmental contamination.
- Drug reservoir or matrix: This layer contains the active pharmaceutical ingredient either dissolved or dispersed within a polymeric matrix that controls the rate of drug release.

- Rate-controlling membrane (in reservoir-type patches): It regulates the rate at which the drug diffuses from the reservoir to the skin surface.
- Adhesive layer: It ensures that the patch adheres securely to the skin during application and may also contain the drug in drug-in-adhesive systems.
- Release liner: A protective layer that is removed before application to expose the adhesive surface.

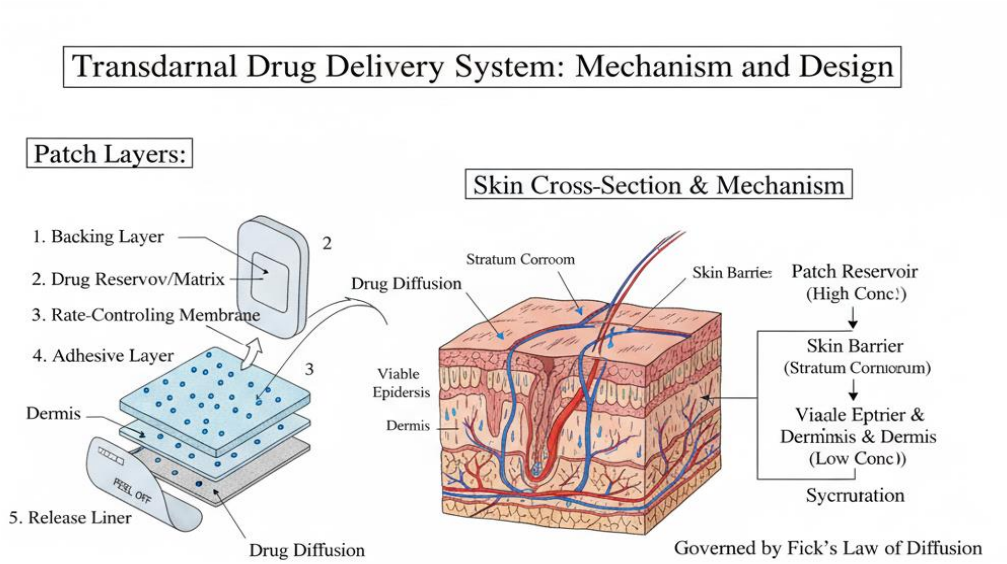

Figure 2: Mechanism and Design of Transdermal Drug Delivery System.

Transdermal patches offer several advantages over traditional delivery methods. They bypass hepatic first-pass metabolism and gastrointestinal degradation, leading to improved bioavailability and reduced systemic toxicity. They provide controlled and sustained drug release, ensuring steady therapeutic levels and minimizing fluctuations in plasma concentration. The non-invasive nature of patches enhances patient comfort and compliance, particularly for chronic therapies. Additionally, treatment can be easily terminated by removing the patch, allowing for flexible dose adjustment and safety.

Physicochemical and Biological Considerations for Transdermal Delivery

The transdermal route offers a non-invasive and convenient method for systemic drug delivery; however, its effectiveness is heavily influenced by both physicochemical properties of the drug and biological characteristics of the skin. The skin, particularly the stratum corneum, acts as a formidable barrier to drug penetration. It consists of densely packed corneocytes embedded in a lipid matrix, making it selectively permeable. Therefore,

successful transdermal drug delivery requires careful consideration of factors that govern drug absorption, permeation, and retention.

Ideal Physicochemical Properties of a Drug for Transdermal Delivery

1. **Molecular Weight:** Should generally be less than 500 Daltons to allow easy diffusion through the stratum corneum.
2. **Lipophilicity (Log P):** Ideally between 1 and 4 to balance penetration through the lipid-rich stratum corneum and partitioning into the aqueous viable epidermis and dermis.
3. **Solubility:** Must be adequately soluble in both lipid and aqueous phases to maintain a concentration gradient and facilitate transport across skin layers.
4. **Hydrophilic-Lipophilic Balance:** Drugs too lipophilic may remain trapped in the stratum corneum, whereas highly hydrophilic drugs may fail to traverse the lipid barrier.
5. **Potency:** Drugs should be potent, as only small amounts can permeate through the skin to achieve therapeutic plasma concentrations.
6. **Melting Point:** Low to moderate melting point (<200°C) is preferred, as high melting point compounds have reduced solubility and skin permeability.
7. **Stability:** The drug should be chemically and physically stable in the formulation and during storage to ensure efficacy.
8. **pKa/Ionization:** Preferably non-ionized or weakly ionized at physiological pH to enhance skin permeation.
9. **Partitioning Ability:** Should easily partition between the formulation vehicle, stratum corneum, and underlying tissues to reach systemic circulation.
10. **Non-Irritant Nature:** Ideally, the drug should not cause skin irritation, sensitization, or allergic reactions to ensure patient compliance.

Skin Anatomy and Barriers to Drug Permeation

The skin is the largest organ of the human body and serves as a critical protective barrier between the internal environment and external factors. It is composed of three primary layers: the epidermis, dermis, and hypodermis, each with distinct structure and function. The epidermis is the outermost layer and is primarily responsible for barrier function. Beneath it lies the dermis, a thick connective tissue layer that provides structural support, houses blood vessels, lymphatics, and nerve endings, and facilitates systemic absorption of drugs.[19] The innermost hypodermis consists mainly of adipose tissue, serving as an energy reservoir and insulation layer.[20]

Within the epidermis, the stratum corneum is the most significant barrier to transdermal drug delivery. It is approximately 10–20 µm thick and consists of terminally differentiated, keratin-rich corneocytes embedded in a dense intercellular lipid matrix.[19,21] This unique "brick-and-mortar" arrangement makes the stratum corneum highly selective, allowing only certain molecules to penetrate while preventing the entry of pathogens, toxins, and excessive water loss. The corneocytes act as the "bricks," providing structural rigidity, whereas the lipids—primarily ceramides, cholesterol, and free fatty acids form the "mortar," which creates a hydrophobic environment that limits the passage of hydrophilic molecules.[19,20]

The stratum corneum's barrier function is influenced by several factors, including thickness, hydration, lipid composition, and age-related changes. Hydration increases permeability by swelling the corneocytes and loosening the lipid packing, while regions with thinner skin, such as the inner forearm or behind the ear, allow greater drug penetration compared to thicker areas like the soles or palms. In addition to the stratum corneum, other minor barriers include tight junctions in the viable epidermis, which further regulate paracellular drug movement.[21,22]

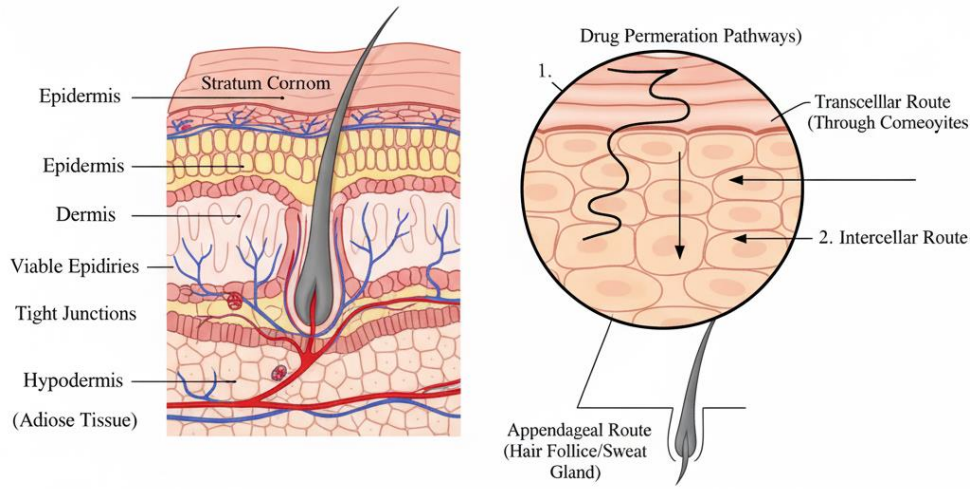

Figure 3: Skin Anatomy and Barriers to Drug Permeation.

Drugs permeate the stratum corneum through three primary pathways: intercellular (between corneocytes), transcellular (through corneocytes), and appendageal routes (via hair follicles and sweat glands). The intercellular route is the most common for small lipophilic molecules, while hydrophilic drugs may preferentially utilize appendageal pathways, although these constitute a minor fraction of the total skin surface. The drug's molecular size, lipophilicity, and solubility dictate its ability to traverse these pathways efficiently.

Methods of Preparation of Transdermal Patch

A. Solvent Casting Method

The solvent casting method is one of the most commonly used techniques for preparing transdermal patches due to its simplicity, reproducibility, and ability to produce uniform films. This method involves dissolving the polymeric matrix in a suitable solvent, incorporating the drug and other excipients, and casting the mixture into thin films. The following steps outline the process in detail.[26]

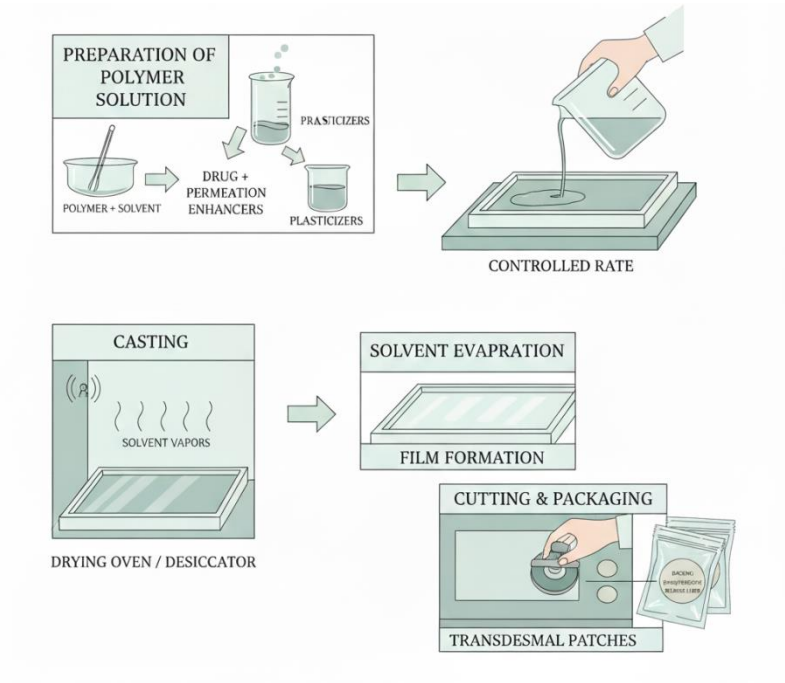

Figure 4: Solvent Casting Method.

1. **Polymer Dissolution:** The selected polymer or combination of polymers (e.g., hydroxypropyl methylcellulose, polyvinyl alcohol, or ethyl cellulose) is dissolved in a suitable solvent, such as ethanol, water, or a mixture of solvents, to form a homogeneous polymer solution. The choice of polymer depends on the desired flexibility, mechanical strength, and drug release characteristics of the final patch.[26]
2. **Addition of Plasticizer:** A plasticizer, such as glycerin, propylene glycol, or polyethylene glycol, is added to the polymer solution to improve the flexibility and mechanical properties of the film. The mixture is stirred continuously until a uniform solution is obtained. Plasticizers help prevent brittleness and cracking of the patch during handling and application.[26,27]
3. **Incorporation of Drug and Permeation Enhancer:** The NSAID and any required permeation enhancers (e.g., oleic acid, DMSO, or terpenes) are uniformly dispersed into

the polymer-plasticizer solution. Proper mixing ensures even drug distribution throughout the film, which is critical for consistent therapeutic efficacy.[27]

4. **Casting the Solution:** The homogeneous drug-polymer solution is poured or cast onto a flat, non-adhesive surface, such as a glass plate or a silicone-coated release liner. The thickness of the cast solution can be controlled using a casting knife or spreader to achieve uniform patches.[28]
5. **Drying:** The cast solution is allowed to dry at room temperature or in an oven at a controlled temperature to evaporate the solvent gradually. Slow drying prevents the formation of air bubbles and ensures smooth, uniform films.[28]
6. **Cutting into Patches:** Once dried, the film is peeled from the surface and cut into patches of the desired size and shape, depending on the intended dose and application area.[27]

B. Melt Casting Method

One popular process for creating transdermal patches is melt casting, which works especially well for medications that are heat-stable. This approach is less harmful to the environment and lowers the possibility of residual solvent toxicity because it doesn't require organic solvents like solvent casting does.[29] Melting the plasticizer and polymer, adding the medication, and then hardening the mixture into homogeneous patches are the steps in the procedure.

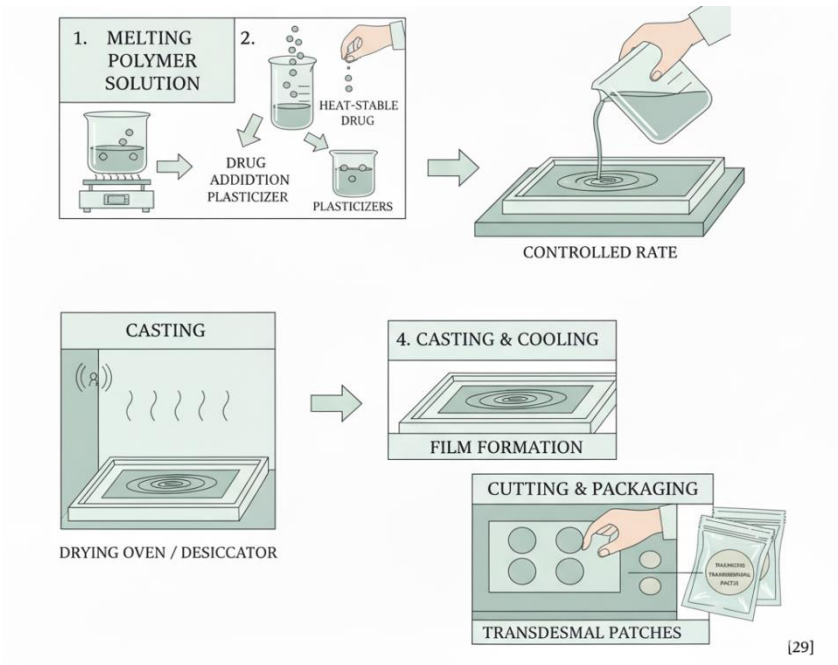

Figure 5: Melt Casting Method.

1. **Melting Polymer and Plasticizer:** The selected polymer (e.g., ethyl cellulose, polyvinyl alcohol, or polyethylene oxide) is heated to a temperature above its melting point. A plasticizer, such as glycerin, propylene glycol, or polyethylene glycol, is added simultaneously to improve the flexibility and mechanical properties of the final patch. The polymer-plasticizer mixture is stirred continuously to form a homogenous molten mass.[27,29]
2. **Incorporation of Drug and Permeation Enhancer:** The NSAID and any permeation enhancers (e.g., oleic acid, menthol, or DMSO) are mixed into the molten polymer. Uniform dispersion of the drug ensures consistent dose distribution throughout the patch, which is critical for maintaining therapeutic efficacy.[28]
3. **Pouring into Mold:** The homogenous drug-polymer mixture is carefully poured into pre-designed molds or onto a flat surface to achieve the desired patch thickness and shape. The mold can be made of silicone, glass, or metal, depending on the ease of removal and thermal stability.[26,30]
4. **Cooling and Solidification:** The filled molds are allowed to cool at room temperature or under controlled conditions. During this stage, the molten polymer solidifies into a flexible film that retains the embedded drug uniformly. Slow cooling is recommended to prevent air bubbles, cracks, or uneven surfaces in the patch.[31]
5. **Application of Backing Layer:** After solidification, an impermeable backing membrane can be applied to protect the patch from environmental factors, enhance mechanical strength, and ensure proper adhesion to the skin.[29]
6. **Cutting into Patches:** Finally, the solidified film is removed from the mold and cut into patches of the desired size and shape, ready for use or further packaging.[29]

C. Adhesive (Drug-in-Adhesive) Method

The Adhesive Method, also known as the Drug-in-Adhesive (DIA) technique, is one of the most commonly employed and commercially successful approaches for preparing transdermal therapeutic systems (TTS).[32] In this method, the drug is directly incorporated into the pressure-sensitive adhesive (PSA) layer that serves both as the drug reservoir and the adhesive matrix for skin application. This process is relatively simple, solvent-efficient, and suitable for large-scale manufacturing.

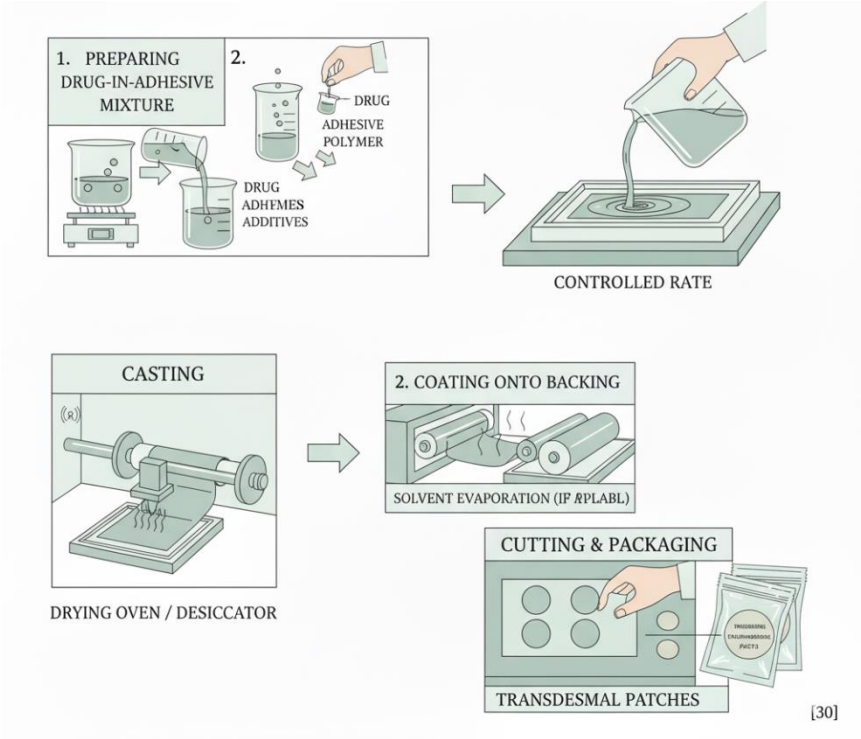

Figure 6: Adhesive (Drug-in-Adhesive) Method.

1. **Dissolution of Drug in Adhesive Matrix:** The selected NSAID is dissolved or uniformly dispersed within a pressure-sensitive adhesive such as polyisobutylene, silicone-based, or acrylic adhesive. The adhesive acts as the drug carrier, providing intimate contact with the skin and allowing controlled diffusion of the drug. If the drug has limited solubility in the adhesive, a suitable solvent (e.g., ethanol, isopropanol, or ethyl acetate) may be used to facilitate uniform mixing. In some cases, permeation enhancers or stabilizers are added to improve drug release and skin permeation.[32,33]
2. **Spreading the Adhesive-Drug Mixture on Release Liner:** The resulting homogeneous drug-adhesive mixture is spread uniformly onto a release liner, typically made of a non-stick material such as silicone-coated polyester film. The thickness of the adhesive layer is carefully controlled to ensure consistent drug loading and release rate. This layer acts as the contact surface during patch application.[33]
3. **Drying and Lamination:** The coated release liner is then dried at controlled temperature to remove any residual solvent, ensuring a uniform and stable adhesive film. After drying, the film is laminated with a backing layer usually an impermeable material such as polyethylene, polyester, or aluminized film which provides mechanical support and prevents drug loss or moisture entry.[34]

4. **Cutting into Patches:** The laminated sheet is finally cut into individual patches of the desired size and shape. These patches can then be packaged with a protective cover to maintain stability until use.[32]

Challenges and Limitations of Transdermal Delivery of NSAIDs

Despite the numerous advantages offered by transdermal drug delivery systems (TDDS) for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), several challenges and limitations still hinder their widespread clinical application and commercialization.[35] These challenges arise primarily from the complex nature of the skin barrier, formulation stability issues, and manufacturing constraints associated with advanced delivery systems.[36]

Limited Permeability of Certain NSAIDs:

One of the major challenges in transdermal delivery is the restricted permeability of drugs through the stratum corneum, the outermost layer of the skin. Many NSAIDs possess high molecular weight, low lipophilicity, or poor solubility, making it difficult for them to diffuse effectively across the skin.[37] Drugs such as diclofenac and ibuprofen have been formulated successfully, but others like indomethacin and naproxen face limitations due to insufficient transdermal flux. Even with permeation enhancers or novel carriers, achieving therapeutic plasma levels can be challenging, especially for drugs requiring higher systemic concentrations.[39]

Variability in Skin Characteristics Among Individuals:

The anatomical and physiological differences in skin structure among individuals can significantly affect transdermal drug absorption. Factors such as age, gender, race, hydration level, body site of application, and skin condition (e.g., dryness, damage, or disease) influence the permeability and drug diffusion rate.[38] For instance, aged or thickened skin tends to have lower permeability, while damaged skin may lead to unpredictable absorption or irritation. This inter-individual variability complicates dose standardization and can result in inconsistent therapeutic responses.[39]

Stability Issues of Novel Delivery Systems

Advanced formulation approaches such as liposomes, niosomes, ethosomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) offer improved permeability and controlled release but are often prone to stability problems.[57] These include particle aggregation, drug leakage, phase separation, and degradation of lipids or polymers over time.

Additionally, maintaining drug stability during storage and ensuring uniformity in large-scale production remain critical challenges. The inclusion of volatile solvents or permeation enhancers can further complicate the stability of transdermal systems.[40]

Cost and Scalability of Nanocarrier-Based Formulations

Although nanocarrier-based transdermal systems show promising results in enhancing skin penetration and drug bioavailability, their high production cost and complex manufacturing requirements limit commercial feasibility.[41] Techniques such as nanoprecipitation, high-pressure homogenization, and lyophilization require specialized equipment and strict quality control, increasing production costs. Moreover, scaling up these formulations while maintaining consistency in particle size, drug entrapment efficiency, and release kinetics poses additional challenges for pharmaceutical industries.[40]

CONCLUSION

Many of the drawbacks of traditional oral and parenteral modes of administering non-steroidal anti-inflammatory medications (NSAIDs) have been addressed by transdermal drug delivery systems (TDDS), which have become a viable and patient-friendly method. Because of systemic exposure and first-pass metabolism, NSAIDs can cause renal damage, hepatic dysfunction, and gastrointestinal irritation even if they are useful in treating pain, inflammation, and fever. Bypassing hepatic metabolism, minimizing gastrointestinal adverse effects, and guaranteeing sustained and controlled drug release, the transdermal route provides a non-invasive substitute that enhances therapeutic efficacy and patient compliance. The physicochemical qualities of the medication, such as its molecular weight, lipophilicity, and solubility, as well as the biological traits of the skin barrier, especially the stratum corneum, have a major role in the success of a transdermal formulation. The permeability and bioavailability of NSAIDs through the skin have been greatly enhanced by advancements in formulation technologies, including vesicular systems (liposomes, niosomes, and ethosomes), nanocarriers (SLNs and NLCs), and penetration augmentation approaches (chemical, physical, and biological). Transdermal patches have drawn a lot of interest among different formulation strategies because of their simplicity of use, accurate dosage management, and capacity to sustain steady-state plasma concentrations over prolonged periods of time.

Large-scale commercialization is still hampered by factors such formulation stability problems, inter-individual variability in skin features, the restricted skin permeability of

certain NSAIDs, and the high production costs of sophisticated delivery systems. To get over these restrictions, future studies should concentrate on refining nanocarrier-based systems, investigating new biocompatible polymers, and incorporating intelligent technologies like iontophoretic or microneedle arrays.

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