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**Review Article**

# A Review Of Transdermal Patch For Management Of Pain

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## ABSTRACT

Transdermal delivery was non-invasive method of administering medication via skin's surface. It may distribute medication throughout the dermis at a predefined pace to provide either a localized or systemic impact. It may be used as a substitute for hypodermic injections and medication administration via mouth. Since most diseases are linked to either severe or moderate pain, analgesics are often utilized for a variety of illnesses. Analgesic patch usage as a pain reliever is currently being often employed. An adhesive patch containing medication used to alleviate mild to moderate pain is called a transdermal analgesic or pain relief patch. patches are now available for a variety of opioids and non-opioid analgesics. antianginal medications and local anesthetics. Buprenorphine, ketoprofen, diclofenacepolamine, piroxicam, capsaicin, nitroglycerine, and lignocaine are among medications. They may be obtained as reservoir patches or as matrix patches. This overview examines many medications used to treat pain, as well as frequency, side effects, and mode of administration of each medication.

## INTRODUCTION

For more than a decade, transdermal medicine delivery patches have been available on market [1]. Majority of transdermal medication delivery patches on the market are retail-only nicotine patches, which aid in quitting smoking. Transdermal patches were first developed to treat motion sickness in astronauts destined for space [2]. A transdermal patch is used to penetrate the skin and enter the bloodstream to provide a prescribed dosage of medicine. The FDA authorized transdermal patch devices for the first time in 1981. Nowadays, transdermal administration systems including scopolamine (hyoscine) for motion sickness, nitroglycerin and clonidine for cardiovascular illness, fentanyl for persistent pain, and nicotine to help with quitting smoking are available. Transdermal delivery prevents pulsed entrance into systemic circulation, permits continuous input of medications with short biological half-lives, and enables regulated, continuous drug administration. Comparing TDDS to oral and traditional injectable techniques, there are several benefits. It lessens the strain that

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eating orally often puts on the liver and digestive system. It improves patient compliance and reduces negative pharmacological side effects brought on by transient overdoses. It can be especially useful for fixes that only need to be applied once a week. Such a basic plan for dosage helps patients follow their medication regimen [3]. Transdermal medications will keep becoming more and more popular as long as safety and effectiveness are progressively enhanced. Another significant advancement will be the creation of patches that release peptide and even proteins found in insulin, growth hormone, and immunizations [4]. There are three types of transdermal patches: first generation, second generation, and third generation.

**First generation transdermal patches**

They are original patches and have seen a lot of usage in medical facilities.medication is contained in a reservoir in the transdermal patch design, which is sealed on one side that comes into touch with skin, using glue and an impermeable backing [4]. Unfortunately, not all medications with right qualities can be supplied because of certain restrictions. stratum corneum, skin barrier, is main area where first generation transdermal patches are restricted. Therefore, medications have to be lipophilic, low molecular weight, and effective at low concentrations.

**Second generation transdermal patches**

advancements in patches that improve skin permeability, lessen harm to deeper tissues, and improve skin absorption. A few adjustments, such pharmacological boosters, non-cavitation ultrasonography, and iontophoresis have thrown off equilibrium in strategy to boost delivery while simultaneously safeguarding deeper tissues at a deeper level.

**Chemical enhancers:**

they introduce amphiphilic molecules to aid improve penetration, upsetting stratum corneum's highly organized bilayer. However, this may irritate your skin.

**Iontophoresis –**

they involve administration of drugs into the stratum corneum under low voltage current. They do not disturb the skin barrier, so they can be used for small molecules that carry a charge and some macromolecules up to a few Daltons. Rate of drug delivery can be controlled using a microprocessor.

**Non-cavitation ultrasound:**

Physical therapists have shown that using ultrasound to massage anti-inflammatory drugs into skin will boost agent's effectiveness as a skin permeation enhancer [5]. consequences areultrasonography has only been used on tiny lipophilic compounds. Because of accompanying tissue heating that might harm deeper tissue, it has been restricted.

**Third generation transdermal patches**

It entails further developments to enhance way medications penetrate skin and safeguard deeper tissues. Human clinical trials have used thermal ablation, microneedles, and microdermabrasion. trials to provide vaccinations, medicinal proteins, and macromolecules.

**DELIVERY FACTORS FOR TRANSDERMAL DRUG**

A number of variables, including the drug's size (<500 Da), pH, skin moisture level, formulation stability, and lipid solubility, affect transdermal drug delivery. The concentration differential between system's saturated drug solution and skin's much lower concentration provides energy needed for drug release; drug transport happens by diffusion[6].

**TRANSDERMAL PATCHES' BENEFITS**

- For many valid reasons, they are favored over the oral route of medication delivery to systemic circulation;
- There is an improvement and increase in bioavailability.

- Patients have trouble swallowing capsules and tablets, and some are inclined to smash tablets in an attempt to make swallowing easier, which eliminates tablet's controlled release properties.
- They are better than hypodermic injections, which hurt more, waste more medical supplies, and increase chance of spreading illness [7].
- increased patient compliance as the procedure is non-invasive, easy to use, and convenient, and since stopping the medication by removing the patches gives patients more freedom [8].
- When medications are administered subcutaneously, there may be less variation and a decrease in concentration of the drug spike that occurs after oral administration [8].

**TRANSDERMAL PATCHES: DISADVANTAGES:**

Along with the benefits come a few drawbacks that in certain circumstances make it unreliable and cumbersome.

- **AGE:**

It has little bearing on how medications are delivered. However, it might be challenging to guarantee sufficient and long-lasting adhesion when dealing with small babies. Because they are more dependable and skin irritation might be less of an issue, they are more favored for older people. Sites of application: penetration varies depending on application site. For instance, skin in genital, palm, and face regions is more permeable than skin in trunk area, which is less permeable.

- When medication comes into occlusive contact with skin, it works better. primary cause of this is elevated subcutaneous hydration brought on by skin's natural barrier to transepidermal water evaporation [9].
- Furthermore, this approach can only deliver a limited quantity of drugs—up to a few hundred Daltons. Moreover, hydrophilic medication delivery has proven challenging.

**METHODS EMPLOYED IN CREATION OF TRANSDERMAL PATCH [10-14]:**

1. **Single-layer Drug-in-Adhesive:**


Direct medication inclusion inside skin-contacting adhesive is the defining feature of single-layer drug-in-adhesive technology.Using a single backing film that houses medicine and all of the excipients, adhesive in this transdermal system design acts as both a skin-attaching agent and basis for formulation. Diffusion over skin determines pace at which drugs are released from this kind of device.

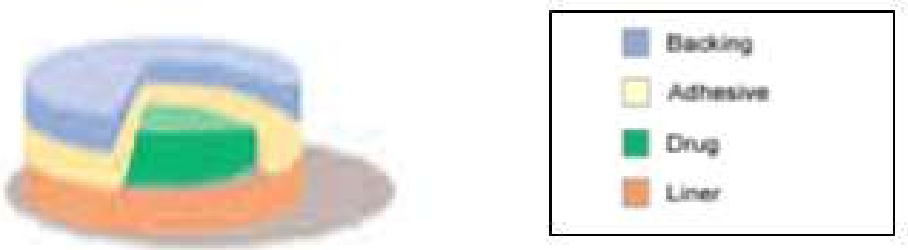
**2. Multi-layer Drug-in-Adhesive:**


Since medication is mixed right into adhesive, Multi-layer Drug-in-Adhesive and Singlelayer Drug-in-Adhesive are comparable. On other hand, term "multi-layer" refers to insertion of a membrane between two separate drug-in-adhesive layers or to insertion of many drug-in-adhesive layers grouped together under a single backing film.

**3. Drug Reservoir-in-Adhesive:**


A liquid compartment holding a medication solution or suspension and kept apart from release liner by an adhesive and semi-permeable membrane define Reservoir transdermal system design. product's adhesive ingredient, which causes skin adherence, may be added in two different ways: either continuously between the membrane and release liner, or in a concentric pattern all around membrane.

**4. Drug Matrix-in-Adhesive:**




A semisolid matrix holding a medication solution or suspension in direct contact with release liner characterizes the design of the Matrix system. skin-adhering component is integrated into an overlay and surrounds semisolid matrix in a circular pattern.

**EVALUATION OF TRANSDERMAL PATCHES**

1. **Thickness of the patch:**

Using a digital micrometer, thickness of drug-loaded patch is measured at various sites, and the average thickness and standard deviation are calculated to guarantee the thickness of ready-made patch. Transdermal film thickness is measured at several places along film using a micrometer, screw gauge, or moving microscope dial gauge [15,16].

2. **Weight uniformity:**

Before testing, the created patches are dried for four hours at 60°C. A predetermined patch area has to be divided into many sections and weighed using a digital balance. The standard deviation and average weight Values must be computed using each weight separately [16].

**3. Folding endurance:**

An area-specific strip is to be cut uniformly, then folded in same spot repeatedly until it breaks. value of folding endurance is determined by number of times film could be folded in the same way without breaking [17].

**4. Percentage Moisture content:**

Each film must be weighed separately and placed in desiccators with fused calcium chloride at room temperature for 24 hours. After this period, the films should be reweighed, and the percentage moisture content can be calculated using the formula provided below [16,18].

**% Moisture content = Initial weight – Final weight X 100**

**5. Content uniformity test:**

10 patches are chosen, and the content of each patch is measured individually. If 9 out of 10 patches fall within 85% to 115% of the specified value, and one falls between 75% to 125% of the specified value, then the transdermal patches meet the content uniformity criteria. However, if 3 patches fall within the 75% to 125% range, then an additional 20 patches are tested for drug content. If these 20 patches range from 85% to 115%, then the transdermal patches pass the content test [18,15].

**6. Moisture Uptake:**

A defined patch area is dissolved in an appropriate solvent at a specific volume. Subsequently, the resulting solution is filtered through a filtration medium, and the drug content is analyzed using the suitable method, either UV or HPLC technique. Each value presented represents the average of three distinct samples [17, 15].

**% moisture uptake = Final weight – Initial weight X 100**

**Initial weight**

**7. Drug content:**

The procedure involves dissolving a designated patch area in a specific volume of an appropriate solvent. Next, the solution undergoes filtration using a filter medium, followed by analysis of the drug content using a suitable method such as UV or HPLC technique. Each value obtained represents the average across three separate samples [14,17].

**8. Water vapor transmission studies (WVT)**

To determine the Water Vapor Transmission (WVT), start by weighing one gram of calcium chloride and placing it in previously dried empty vials with equal diameters. Paste polymer films over the vial brims using an adhesive like silicon adhesive grease, allowing the adhesive to set for 5 minutes. Subsequently, accurately weigh the vials and position them in a humidity chamber maintained at 68% Relative Humidity (RH). Weigh the vials again at the end of each day for seven consecutive days. Any weight increase indicates the amount of moisture transmitted through the patch. Alternatively, in another method, desiccators are employed to house the vials. Inside these desiccators, 200 mL of saturated sodium bromide and potassium chloride solution is placed. The desiccators are sealed tightly, and humidity levels inside are measured using a hygrometer. The weighed vials are then placed in the desiccators, and the procedure is repeated accordingly.

$$\mathbf{WVT = W/ ST}$$

W represents the weight gain within a 24-hour period; S indicates the exposed area of the film in square centimeters ($cm^2$); and T signifies the duration of exposure [19].

**9. In vitro drug release studies**

The paddle over disc method (USP apparatus V) is used to evaluate the drug release from the

prepared patches. Dry films of known thickness are cut into specific shapes, weighed, and affixed onto a glass plate using adhesive. This glass plate is then immersed in a 500-mL volume of dissolution medium or phosphate buffer solution (pH 7.4), and the apparatus is stabilized at 32±0.5°C. The paddle is positioned 2.5 cm away from the glass plate and operated at 50 rpm. Samples (5-mL aliquots) are withdrawn at appropriate intervals up to 24 hours and analyzed using either a UV spectrophotometer or HPLC. The experiment is conducted in triplicate, and the mean value is calculated from the obtained data [20].

**10. In vitro skin permeation studies**

An in vitro permeation study can be conducted using a diffusion cell. For this, full-thickness abdominal skin from male Westar rats weighing between 200 to 250g is utilized. The abdominal hair is carefully removed using an electric clipper. The dermal side of the skin is then cleansed thoroughly with distilled water to eliminate any adhering tissues or blood vessels. It is subsequently equilibrated for an hour in a dissolution medium or phosphate buffer at pH 7.4 before initiating the experiment. The skin sample is then placed on a magnetic stirrer with a small magnetic needle to ensure uniform distribution of the diffusant. The temperature inside the cell is maintained at 32 ± 0.5°C using a thermostatically controlled heater.The isolated rat skin piece is mounted between the compartments of the diffusion cell, with the epidermis facing upwards into the donor compartment. At regular intervals, a specific volume of sample is withdrawn from the receptor compartment, and an equal volume of fresh medium is replenished. These samples are filtered through a filtering medium and can be analyzed either spectrophotometrically or by HPLC.The flux is directly determined as the slope of the curve between the steady-state values of the amount of drug permeated (mg cm-2) versus time in hours. Permeability coefficients are then deduced by dividing the flux by the initial drug load (mg cm-2) [20,21,22].

**11. Skin Irritation study**

Skin irritation and sensitization testing can be conducted on healthy rabbits with an average weight ranging from 1.2 to 1.5 kg. The dorsal surface of the rabbit, measuring 50 $cm^2$, is prepared by cleaning and removing hair through shaving. The area is then cleansed using rectified spirit. Representative formulations are applied to the cleaned skin. After 24 hours, the patch is removed, and the skin is observed and classified into 5 grades based on the severity of skin injury [23].

**PAIN MANAGEMENT USING TRANSDERMAL PATCHES:**

Transdermal patches have become a staple in pain management, addressing both acute and chronic pain. They come in diverse types like non-steroidal anti-inflammatory drug patches (NSAID), opioid patches, local anesthetic patches, capsaicin, and nitroglycerine, finding widespread use even in pediatric care.

**1. NSAIDs Patches:**

NSAIDs are widely used medications for managing both chronic and acute musculoskeletal conditions [24]. Their advantage lies in their localized action, avoiding central adverse effects and cognitive impairments. Various commercially available NSAID patches include ketoprofen, diclofenac, flurbiprofen, and piroxicam patches [25]. The objective of topical NSAIDs is to reduce systemic adverse effects and promote adherence. A systematic review involving 3455 subjects examining topical NSAIDs for acute musculoskeletal conditions (like strains and overuse injuries) concluded that these formulations offer significant pain relief without the systemic side effects associated with oral NSAIDs [26].

The most commonly used NSAID patch is the 1% diclofenac epolamine patch, approved for treating acute pain in conditions like epicondylitis and ankle sprains. Recent reviews support its use for both topical and systemic effects [27]. Patients with ankle sprains showed reduced pain scores after 3 hours, likely due to its local analgesic action as diclofenac appears in the bloodstream approximately 4.5 hours after topical application. After patch removal, a local reservoir effect prolongs diclofenac's presence in the plasma for around 9-12 hours, compared to 1-2 hours with oral intake. Systemic transfer after patch removal is minimal (about 2%), significantly reducing systemic side effects compared to oral forms. Ketoprofen, available as both a patch and gel, is another prominent NSAID. Besides inhibiting COX enzymes, it stabilizes lysosomal membranes and counteracts bradykinin, providing better pain relief and functional improvement in patients with rheumatic diseases or trauma compared to placebo [28]. Side effects are primarily related to the patch and are cutaneous, not from the active ingredient.

Piroxicam, a potent NSAID with analgesic and antipyretic effects, finds use in various musculoskeletal and joint disorders, including rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, soft tissue disorders, acute gout, and post-operative pain [29]. Its high solubility and permeation properties enhance its efficacy.

**2. Opioid Patches:**

Opioid analgesics are prescribed for moderate to severe pain, particularly of visceral origin, recommended for non-cancerous conditions only when prescribed by a physician. Opioid patches consist of a drug reservoir separated from the skin by a membrane, releasing the drug gradually. Fentanyl and buprenorphine patches are common opioid patches due to their high lipid solubility and low molecular weight, facilitating dermal penetration. Fentanyl, a potent short-acting narcotic analgesic, is widely used for chronic pain control via transdermal patches, including palliation of malignant pain. Its properties allow it to penetrate the skin efficiently, maintaining a constant plasma concentration over 72 hours of application, with peak concentrations between 12 and 24 hours. Heat exposure can enhance fentanyl delivery. These patches improve pain control and quality of life in chronic pain conditions like osteoarthritis or rheumatoid arthritis [30]. They are particularly useful when oral morphine isn't viable due to renal impairment or swallowing difficulties [31]. Some studies even suggest fentanyl patches are more effective than oral morphine in cancer pain management. However, fentanyl patches should not be used in opioid-naïve patients with non-cancer pain due to potential serious adverse effects. They have a delayed onset and prolonged duration of action and subsequent side effects can be challenging to manage with opioids like fentanyl [32]. Respiratory depression stands out as the most severe side effect linked to fentanyl, along with potential issues like vomiting, nausea, and skin irritation due to patch adhesive. Notably, fentanyl induces less constipation compared to oral morphine [33]. Buprenorphine, derived from thebaine, is a potent opioid with a low molecular weight and lipophilic nature. It's notable for its prolonged action, antihyperalgesic effects, and minimal renal involvement. It proves effective in chronic pain management, providing relief for conditions like osteoarthritis and low back pain [34]. Clinical trials highlight improved pain relief, sleep quality, and reduced need for rescue therapy in cancer pain cases [35]. Typically initiated at a low dose and gradually increased, buprenorphine patches come in strengths of 32, 52.5, and 70 µg/hrs over 72 hours [33]. Although initial studies show enhanced patient compliance over several months, later side effects such as vomiting, nausea, and constipation may arise. However, respiratory depression exhibits a ceiling effect, especially

when combined with central nervous system depressants [36].

**3. Local anesthetic patches**

serve to alleviate discomfort during procedures like venipuncture. They offer fewer side effects and are simple to apply, ideally working with localized action and limited systemic impact [37]. Lidocaine patches, commonly used for postherpetic neuralgia, deliver beneficial pain relief, allodynia reduction, and improved quality of life with minimal adverse effects [38]. Versatis patches, with a dual mode of action, have shown superior pain relief compared to placebo in short-term studies. Capsaicin, derived from chili peppers, is utilized in various medical applications, including neuropathic pain and osteoarthritis [39]. Available as an 8% dermal patch (NGX 4010), capsaicin shows efficacy for conditions like postherpetic neuralgia for up to 12 weeks post-application [40]. Significant side effects of capsaicin patches encompass sensations like burning, stinging, erythema, and edema, potentially leading to progressive neuronal dysfunction. Some users also experience transient hypertension along with local pain [41]. It's crucial to avoid applying capsaicin to open wounds. Despite its long-term effectiveness, the patch's use is now restricted due to the inconvenient side effects experienced by many individuals. Nitroglycerine, an organic nitrate, acts as a potent analgesic and anti-inflammatory agent. Initially used for coronary heart disease, its impact on coronary artery dilation was modest. Marketed as Nitro-Dur and Transderm-Nitro®, its absorption is gradual, maintaining constant plasma levels throughout the day. It starts working in about 30 minutes, offering relief for up to 6 hours. Nitroglycerine has shown effectiveness in treating conditions like rotator cuff lesions and varicose vein sclerosis, reducing acute pain compared to a placebo. Common side effects include headaches, palpitations, allergic reactions, contact dermatitis, and flushing. Abrupt cessation of nitroglycerine can lead to acute myocardial infarction and peripheral ischemia [42]. These patches are recommended for localized pain, particularly in patients unable to use NSAIDs due to their lack of renal, gastrointestinal, and hematological adverse effects [43].

## CONCLUSION:

Transdermal drug delivery presents promising prospects for addressing the challenges associated with low bioavailability of oral medications and the discomfort of injections. Advances in transdermal technology, from first-generation patches to second-generation chemical enhancers and iontophoresis, are enhancing the delivery capabilities for small molecules. Additionally, third-generation physical enhancers hold the potential to facilitate transdermal delivery of larger molecules, such as macromolecules and vaccines. A significant leap forward will come with the development of total dissolved solids units capable of delivering peptides and even proteins like insulin and growth hormone through the skin. This advancement could revolutionize the way we administer complex medications.The transdermal patch is an underutilized tool in managing both acute and chronic pain. With ongoing improvements in delivery mechanisms and an expanding range of analgesics, we anticipate a rise in the popularity and utility of transdermal drug delivery. This modality holds promise for more effective and convenient drug administration in the future.

## FUTURE PROSPECT:

Continued advancements in drug delivery systems will likely lead to more efficient and targeted transdermal patches. These systems may incorporate nanotechnology or microtechnology to enhance drug penetration and efficacy while minimizing side effects. The development of transdermal patches for delivering biological agents such as antibodies, cytokines, or gene

therapies holds significant potential. This could revolutionize pain management by targeting specific molecular pathways involved in pain perception and inflammation. Future transdermal patches may integrate multiple therapeutic agents, such as opioids with non-opioid analgesics or adjuvant medications targeting neuropathic pain mechanisms. These combination therapies could offer synergistic effects and improve overall pain relief. Advancements in wearable technology and sensor integration may lead to the development of "smart" transdermal patches. These patches could monitor pain levels, adjust drug delivery in real-time, and provide feedback to healthcare providers for personalized treatment optimization.

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