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A COMPREHENSIVE REVIEW ON TRANSDERMAL DRUG DELIVERY SYSTEMS FOR PAIN MANAGEMENT: FORMULATION APPROACHES AND CLINICAL PERSPECTIVES

Palak Gupta*[1], Vivek Kumar Singh[2], Amit Bhatt[3], Shivani Sharma[4]

[1,2,3]Scholar, School of Pharmacy and Research, Dev Bhoomi Uttarakhand University.

[4]Assistant professor, School of Pharmacy and Research, Dev Bhoomi Uttarakhand University.

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***Corresponding Author**

Palak Gupta

3Scholar, School of Pharmacy and Research, Dev Bhoomi Uttarakhand University.

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ABSTRACT

Transdermal drug delivery systems (TDDS) represent a modern and patient-friendly approach for pain management, offering several advantages over conventional oral and injectable routes. By delivering medication directly through the skin, these systems avoid first-pass hepatic metabolism, provide steady plasma drug levels, and improve overall therapeutic effectiveness and patient adherence. This review outlines the evolution of transdermal patches and their role in managing acute, chronic, neuropathic, and musculoskeletal pain. Clinically approved synthetic patches such as fentanyl, nicotine, nitroglycerin, clonidine, and lidocaine demonstrate the practical success of this technology. In addition, herbal-based patches containing bioactive compounds like capsaicin, curcumin, menthol, boswellic acid, aloe vera, and gingerol show promising potential for localized therapy with minimal systemic effects. Common formulation techniques, including solvent casting and membrane-based methods, are also discussed. Although limitations such as skin barrier resistance remain, ongoing advancements in polymers, permeation enhancers, and innovative delivery strategies continue to strengthen the future of transdermal pain therapy.

KEYWORDS: Transdermal drug delivery, TDDS, Pain management, solvent casting, membrane -based system, herbal patches.

INTRODUCTION

HISTORY OF TDDS

Transdermal medication administration has existed since the beginning of humanity. Three generations of development have gone into transdermal medication administration, with the third generation utilizing medical equipment and technologies.[1]

In past ages, the application of specific plasters and ointments predicted transdermal medicine delivery. One example is the mustard plaster, which is used at home to treat acute chest congestion. Powdered mustard seed (Brassica nigra) was mixed with warm water to make a paste, which was placed on a strip of flannel and applied to the patient's chest with a cloth binding looped around the torso to keep the plaster in place.

Plasters have a long history that dates back to ancient times. In addition to mustard plasters, numerous other plasters were identified in early twentieth-century editions of the United States Pharmacopeia (USP) and National Formulary. It used to be thought that Belladonna Plaster, which contained 0.25–0.30% belladonna root alkaloids, worked as a transdermal analgesic.[2]

The ancient Egyptians manufactured cosmetics and dermatological items (unguents, creams, pomades, rouges, powders, and eye and nail paints) using oils (like castor, olive, and sesame), fats (mostly animal), scents (such bitter almond, peppermint, and rosemary), and other materials.[3]

The US FDA originally authorized the Transderm-SCOP19 patch in 1979. It was a three-day patch that administered scopolamine to prevent motion sickness. Nearly ten years later, nicotine patches became the first transdermal product to be successful, bringing transdermal delivery to a new level of public and medical awareness. Many transdermal delivery systems are available today to deliver various medications, including fentanyl, testosterone, lidocaine, and estradiol; combination patches that contain multiple drugs for hormone replacement and contraception; and iontophoretic and ultrasonic delivery systems for pain relief.

Although 74% of medications are taken orally, the oral route has been the most popular drug delivery method for decades. However, this method is still not always as successful as expected. While oral administration offers the major benefit of ease of administration, it also has serious disadvantages, including poor bioavailability because of hepatic metabolism (first

pass mechanism) and the tendency to cause abrupt spikes in blood levels (both high and low). In order to overcome these obstacles, a new drug delivery method or system has to be understood and developed. All things considered, these transdermal patches are incredibly convenient, easy to apply, and offer tremendous convenience.[4]

PAIN

Pain is described as a subjective experience connected to prospective or existing tissue injury. There are usually two components: sensory, which is linked to knowledge about unpleasant stimuli, and emotional, which is linked to a patient's response to unpleasant stimuli. This is frequently linked to psychological reactions and a person's sensitivity to pain. Other types of pain: acute, which usually lasts three months, and chronic, which lasts longer.

According to pathophysiology, pain can be classified as either neuropathic (related to disease or damage of the somatosensory nervous system, regardless of the underlying causes) or nociceptive (somatic, visceral), which is linked to damage of various internal organs, the musculoskeletal system, soft tissues, and the skin with intact nervous systems.[5]

Application of transdermal delivery systems in the management of pain

Acute pain

The pain relief patch has two functions in the treatment and prevention of acute pain. A local anaesthetic patch can be applied to create an area of anaesthesia, such as to lessen the discomfort associated with vaccinations or venesections. In paediatric practice, these patches are especially helpful. Acute pain from musculoskeletal injuries can be treated with non-steroidal anti-inflammatory medications (NSAIDs) in patch form.

Chronic pain

For the management of persistent nociceptive pain, transdermal analgesics may be helpful. Patches containing buprenorphine and fentanyl have been on the market for many years. For example, topical capsaicin and lidocaine patches may be useful in the treatment of persistent neuropathic pain due to their localized transdermal distribution.[6] The negative effects of chronic pain issues, such as a patient's quality of life, psychological health, and daily functioning abilities, can be addressed by effective pain therapies, including multimodal techniques.

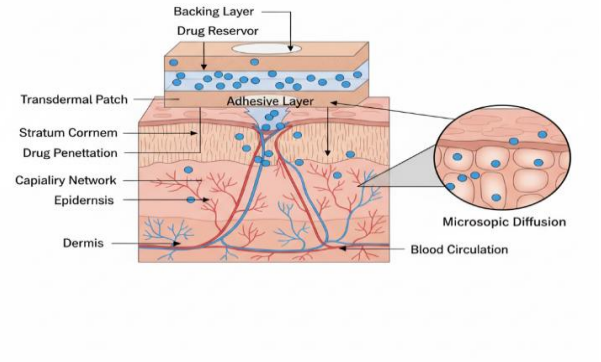
Neuropathic pain

Painful diabetic neuropathy and post-herpetic neuralgia (PHN) are the causes. Neuropathic pain arises from diseases or lesions that impact the somatosensory nerve system, either centrally or peripherally. In clinical terms, neuropathic pain is defined by induced increased pain responses following noxious or non-noxious stimuli, as well as spontaneous continuous or shooting pain.[7]Since FDA-approved topical analgesics have less drug exposure than oral drugs, they may have a more desirable side effect profile. Topical analgesics are also used for neuropathic pain.[8] The current investigation found that the 5% lidocaine patch was a clearly effective add-on therapy for lowering persistent pain and allodynia during the first 8 hours after application. The patches also showed good efficacy over a 7-day period in a variety of focal PNPS.[9]According to a pilot study with 16 patients with different peripheral neuropathies, 81% of the patients experienced moderate to better pain reduction after using a 5% lidocaine patch.[10]

Musculoskeletal

Many musculoskeletal problems, including joint pain, low back pain, neck pain, limb pain, and persistent, all-over pain, are a key reason for primary care consultations. This article utilizes low back discomfort as an example.[11]When applied over unbroken skin, a transdermal patch combining lidocaine and tetracaine (SyneraÒ; Galen US Inc., Souderton, PA) has been demonstrated to give procedural local anaesthetic without the need for an injection.[12]An other medication for musculoskeletal pain that has gained popularity in the emergency department is transdermal lidocaine. By focusing on and inhibiting sodium ion channels in neurons that react to nociception, lidocaine helps to produce analgesia.

Patches containing lidocaine 4% have little adverse effects.[13]



Formulation table 1: Transdermal patch (matrix / drug-in-adhesive type).

Components	Ingredients	Category	Role / Use in Formulation
API	Lidocaine, fentanyl, nitroglycerine	Local anaesthetic drug	Produces local analgesic effect by blocking voltage-gated sodium channels in peripheral nerves; used for management of neuropathic and localized pain
Polymer / Matrix former	Polyacrylate polymer, cellulose derivatives, zein, gelatin, shellac, waxes, gums, Polybutadiene, hydrin rubber, polyisobutylene, Silicone rubber, nitrile, acrylonitrile (acrylic pressure-sensitive adhesive)	Film former / drug matrix	Forms the adhesive matrix that uniformly disperses lidocaine and controls drug release to the skin
Adhesive	Polyisobutylene (PIB) or acrylic PSA	Pressure-sensitive adhesive	Provides adhesion to skin and also acts as a drug reservoir in drug-in-adhesive systems
Plasticizers	Triethyl citrate or Polyethylene glycol (PEG 400)	Plasticizer	Improves flexibility of the patch, prevents cracking, and enhances patient comfort
Penetration enhancer	Propylene glycol, Span 80, Menthol, DMSO, etc	Permeation enhancer / humectant	Enhances penetration of lidocaine across the stratum corneum by increasing skin hydration and drug partitioning
Solvent	Ethanol, Isopropyl alcohol, Chloroform, etc	Solvent	Solubilizes lidocaine and polymers during patch preparation and improves drug diffusion through skin
Backing layer	Polyester, Polypropylene, Polyurethane, vinyl polyethylene etc	Backing membrane	Provides mechanical support, protects formulation, and prevents drug loss to the environment
Release liner	Silicone-coated polyethylene terephthalate (PET), Polyethylene, etc	Protective liner	Protects adhesive surface before application and is removed prior to use

[14], [15], [16], [17], [18]

Methods of preparation

Solvent casting Method

Step 1: Weigh Polymers Accurately

Step 2: Dissolve polymers in a water-methanol mixture (1:1) → Achieve a Transparent Solution

Step 3: Incorporate Drug into Polymer Solution → Mix thoroughly to obtain a Clear Solution

Step 4: Add PEG 400 (Plasticizer)

Step 5: Add Propylene Glycol (Permeation Enhancer)

Step 6: Cast Solution into Glycerin-Greased Petri Dish

Step 7: Cover with Inverted Funnel → Prevent Rapid Solvent Evaporation

Step 8: Dry at Room Temperature (24-48 Hours)

Step 9: Store in a desiccator (After 24 Hours) → Proceed to Further Analysis.[19]

End.

Asymmetric TPX membrane preparation

1. Dissolve TPX polymer in a mixture of cyclohexane (solvent) and nonsolvent additives at 60°C to form a polymer solution.
2. Keep the polymer solution at 40°C for 24 hours to ensure complete Mixing and stability.
3. Cast the polymer solution on a glass plate to a fixed thickness using a Gardner knife
4. Allow the cast film to evaporate at 50°C for 30 seconds (partial drying).
5. Immediately immerse the glass plate with the partially dried film into a coagulation bath maintained at 25°C.
6. Keep the plate in the coagulation bath for 10 minutes to allow formation of the asymmetric TPX membrane.
7. Remove the membrane from the bath and allow it to air-dry
8. Place the membrane in a circulation oven at 50°C for 12 hours for complete drying.[20]

Circular Teflon mould method

1. Prepare a polymer solution by dissolving polymers in an organic solvent in required ratios.
2. Dissolve the calculated amount of drug in half of the same organic solvent.
3. Dissolve skin permeation enhancers (in required concentrations) in the other half of the organic solvent.
4. Add the enhancer solution to the drug–polymer solution.

5. Add di-n-butyl phthalate as a plasticizer into the combined drug-polymer solution.
6. Stir the entire mixture for 12 hours to obtain a uniform solution and remove air bubbles.
7. Pour the final solution into a circular Teflon mould placed on a leveled surface.
8. Cover the mould with an inverted funnel to control the rate of solvent evaporation in a laminar flow hood (air speed ~0.5 m/s).
9. Allow the solvent to evaporate for 24 hours.[20]

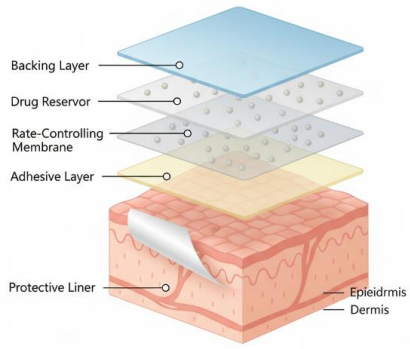


Table 1. Marketed Transdermal Patches Containing Synthetic Drugs: Clinical Uses and Formulation Components.

Drugs Name	Common Brand	General uses	Key Ingredients/Excipients
Nicotine	NicoDerm CQ	Smoking cessation; reduces withdrawal[1]	Deproteinized natural rubber latex (DNRL), sodium carboxymethyl cellulose (SCMC), methyl cellulose (MC), or polyvinyl alcohol (PVA).[2]
Fentanyl	Duragesic[3]	Chronic, severe pain management[4]	Ethanol (enhancer), hydroxyethyl cellulose, polyester backing, ethylene vinyl acetate[4]
Rotigotine	Neupro	Parkinson's Disease and restless legs Syndrome (RLS)[5]	Silicone adhesive ,PVP (inhibitor), Sodium alginate (SA)[6]
Asenapine	Secuado	Treatment of schizophrenia[7]	Isopropyl Palmitate (enhancer), sodium diacetate, rubber –based adhesive agent[7]
Oxybutynin	Oxytrol	Overactive bladder (QAB)[8]	Triacetin, ethanol to facilitate skin permeation, glycerin, which functions as a skin emollient.[8]
Clonidine	Catapres-TTS	Hypertension (High blood pressure).[9]	(Chloroform, Acetone, Glycerol, Propylene Glycol, PEG400, PEG200, Caster Oil, Dibutyl phthalate, Potassium

			dihydrogen phosphate, Sodium hydroxide, Ammonia solution, Tween80, Eucalyptus oil and Ethyl cellulose)[9]
Scopolamine	Transderm Scop	Prevention of motion sickness and nausea[10]	Acetonitrile, ethanol, hydroxypropyl cellulose (HPC)[11]
Nitroglycerin	Nitro-Dur	Prevention of Angina Pectoris (chest pain)[12]	Polyethylene glycol (9PEG is crosslinking polymer), Acrylic-acid matrices, Cellulose derivatives (Polyvinylpyrrolidone)[13]

[21], [22], [23], [24], [25], [26], [27], [28], [29], [30], [31], [32], [33]

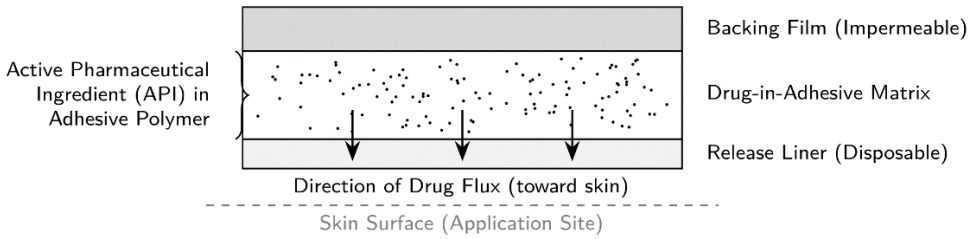
Table 2. Marketed Transdermal Patches Containing Herbal Drugs: Clinical Uses and Formulation Components

Drugs/Herbs Name	Common Brand/Product Type	General Uses	Key Active Phytoconstituents	Excipients/Polymers Used
Capsaicin (Capsicum annuum	Qutenza, Salonpas	Neuropathic Pain, Post-herpetic neuralgia[1]	Capsaicinoids (Capsaicin, Dihydrocapsaici)	silicone matrix carriers, crosslinkable polydimethylsiloxane-(α, ω)–divinyl, glycerol, polysorbate 20[2]
Curcumin (Curcuma Longa)	Turmeric Healing Patch	Wound healing, Anti-Inflammatory	Curcuminoids (Curcumin I, II, III	Chitosan and tripolyphosphate, HPMC, EC n10, chloroform, polyethylene glycol 400 (PEG 400)[3]
Menthol (Mentha Piperita)	Icy Hot, Tiger Balm Patch	Musculoskeletal pain, Cooling effect[4]	L-Menthol, Menthone	polyvinyl alcohol, hydroxypropyl methylcellulose, polyethylene glycol, silicone elastomer and heptane.[5]
Boswellic Acid (Boswellia serrata)	Shallaki Patch	Osteoarthritis, Rheumatoid arthritis, asthma.[6]	beta-Boswellic acid, AKBA, 11-keto-β-boswellic acid (KBA),[6]	Lecithin, Tween 80 (surfactant) PVP, Ethyl Cellulose, Propylene glycol[7]
Aloe Gel (Aloe barbadensis)	Aloe Vera Sooting Patch	Burn, Wound healing, Skin Hydration	Polysaccharides (Acemannan), Anthraquinones, lycoproteins[8]	Ethanol 96% Technical, Carbopol, Triethanolamine (TEA), Phenoxyethanol[9]
Gingerol (Zingiber officinale)	Ginger Pain Relief Patch	Nausea, Joint pain, Arthritis, antioxidant	6-Gingerol, Shogoals, paradols, and zingerone	Arrageenan, sodium deoxycholate, Tween 80, Sodium alginate, Ethanol,

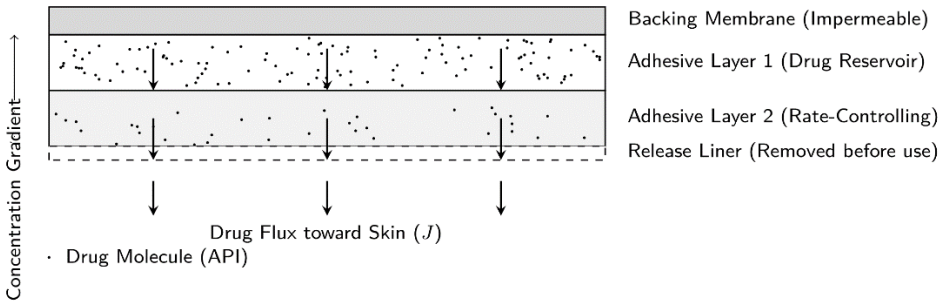
				potassium.[10] dihydrogen phosphate[10]
Shatavari (Asparagus racemosus)	Shatavari Adaptogen Patch	Antimicrobial, anti-inflammatory, and adaptogenic properties[11]	steroidal glycosides, saponins	PEG 4000, PVA, PVP, HPMC K100LV [11]

[34], [35], [36], [37], [38], [39], [40], [41], [42], [43], [44], [45]

Single-Layer Drug-in-Adhesive (DIA) Patch Architecture



Multi-Layer Drug-in-Adhesive (DIA) Patch Architecture



ADVANTAGES

1. It is an easy procedure that only needs to be used once a week. Patient adherence to medication therapy can be improved by such a straightforward dosage schedule.
2. Patients who cannot handle oral dosage forms might be accommodated by using transdermal medication delivery as an alternate method of administration.
3. Patients who are unconscious or experiencing nausea benefit greatly from it.[46]
4. The patch can be removed at any time during therapy to immediately stop drug input in the event of an emergency.
5. It is appropriate to deliver medications through the skin if they exhibit stomach discomfort and absorption delivery system.[47]
6. Less impact on absorption, gastrointestinal drug-drug interactions, and/or dietary effects than oral counterparts.
7. Titration to the best possible dose by modifying the patch application time.

8. Stable medication delivery by efficient regulation of plasma concentrations to prevent episodic peaks.[48]

DISADVANTAGES

1. Local discomfort at the application site.
2. For penetration, the drug's molecular size should be smaller than the skin's pore size.
3. Medications having a high melting point will not melt when heated by the body and will be less soluble.[49]
4. The possibility of adverse reactions, such as itching, rashes, local edema, etc., at the application site.
5. Drugs with larger molecular sizes (over 1000) have trouble being absorbed.
6. The function of the skin's barrier differs depending on the individual.[50]
7. The application location may experience minor discomfort.
8. The medication, the adhesive, or additional excipients in the patch formulation may result in erythema, irritation, and local edema.[51]

CONCLUSION

Transdermal drug delivery has become a highly efficient and convenient method for treating pain, overcoming several drawbacks found in traditional oral or injectable treatments. These patches avoid the issues of digestive breakdown and liver metabolism, instead offering a steady and regulated release of medication. This process ensures consistent levels of the drug in the bloodstream, which boosts effectiveness, minimizes the need for frequent doses, and makes it easier for patients to follow their treatment plans. Furthermore, developments in material science and innovative formulation techniques have broadened the variety of medications that can be successfully administered through the skin.

This review highlights the evolution of transdermal patches from first-generation passive systems to advanced designs incorporating optimized polymers, permeation enhancers, and emerging micro-device technologies. The clinical success of marketed synthetic patches such as fentanyl, nicotine, nitroglycerin, and clonidine demonstrates the effectiveness of transdermal therapy in chronic pain management and other long-term conditions. In parallel, herbal transdermal patches containing bioactive phytoconstituents including capsaicin, curcumin, menthol, boswellic acid, aloe vera, and gingerol have shown promising potential for localized pain relief with reduced systemic side effects. Various formulation methods, such as solvent casting, asymmetric membrane preparation, and circular Teflon mould

techniques, emphasize the importance of polymer selection, plasticizers, permeation enhancers, and controlled processing conditions in achieving effective and reproducible patches. Despite their advantages, transdermal drug delivery systems face challenges related to skin barrier properties, drug physicochemical limitations, inter-individual variability, and possible skin irritation. Overall, transdermal patches represent a valuable and evolving platform for pain management, with ongoing research expected to further enhance their clinical applicability and therapeutic potential.

FUTURE ASPECTS

Future developments in transdermal drug delivery for pain management are expected to focus on improving drug permeation, safety, and patient comfort. Novel polymers, bioadhesive materials, and optimized permeation enhancers will be explored to increase drug transport across the skin while minimizing irritation. The incorporation of nanocarriers and lipid-based systems into transdermal patches may further enhance the delivery of poorly permeable analgesic agents. Emerging physical enhancement techniques, such as microneedles and electrically assisted systems, are likely to expand transdermal therapy to include hydrophilic drugs and macromolecules. In addition, smart and stimuli-responsive patches capable of regulating drug release according to physiological conditions may offer more precise pain control. Greater emphasis will also be placed on the standardization and clinical validation of herbal transdermal patches. Overall, continued innovation and multidisciplinary research will strengthen the role of transdermal systems as safe, effective, and patient-centric options for future pain management.

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