

# Transdermal Drug Delivery in Pain Management

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## **Abstract and Introduction**

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### **Introduction**

Transdermal drug delivery is defined as the non-invasive delivery of medications through the skin surface. The use of analgesics as a 'pain relief patch' is gaining popularity. When applied to the skin, these patches can deliver an analgesic drug at a predetermined rate across the dermis to achieve either a local or systemic effect.

Transdermal delivery of medications is not a new concept. The use of transdermal delivery of homemade medicinal preparations dates to the early 20th century. Mustard plasters were used for severe chest congestion. The Belladonna Plaster, containing 0.25% of Belladonna alkaloid, had a place in the US pharmacopeia as a transdermal analgesic.<sup>[1]</sup> The success of nicotine patches nearly two decades ago revolutionized the use of transdermal drug delivery. Over the last decade, an increasing number of analgesic drugs have become available as transdermal patches.

Patches offer advantages over conventional parenteral or oral routes. They ensure controlled absorption and more uniform plasma drug concentrations. Bioavailability is improved by avoiding first-pass hepatic metabolism and enzymatic or pH-associated deactivation. Delivery of the drug is via a simple and painless application. There is increased flexibility in terminating drug administration by patch removal. Patient compliance is improved as patches are simple, non-invasive, and convenient. Clear labelling ensures rapid identification of medication.

There are, however, some limitations to transdermal drug delivery. First, there may be local irritation or sensitization of the skin at the site of patch application. Secondly, not all drugs are suitable for transdermal delivery. Thirdly, this modality is not suitable for shocked patients as decreased peripheral blood flow leads to unreliable transdermal absorption. Finally, in comparison with other routes of drug delivery, the transdermal route is relatively more expensive.

### **Pharmacokinetics of Transdermal Drug Delivery**

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The drug needs to be present in a high concentration within the patch for transdermal delivery to occur. The energy for drug release is derived from the concentration gradient existing between a saturated solution of drug in the system and the

much lower concentration in the skin; drug movement occurs by diffusion. Since there is a high concentration within the patch and a low concentration in the blood, the drug will continue to diffuse, maintaining a constant concentration of drug in the circulation.

The rate of permeation across the skin is given by:

$$\frac{dm}{dt} = \frac{DCoP}{h}$$

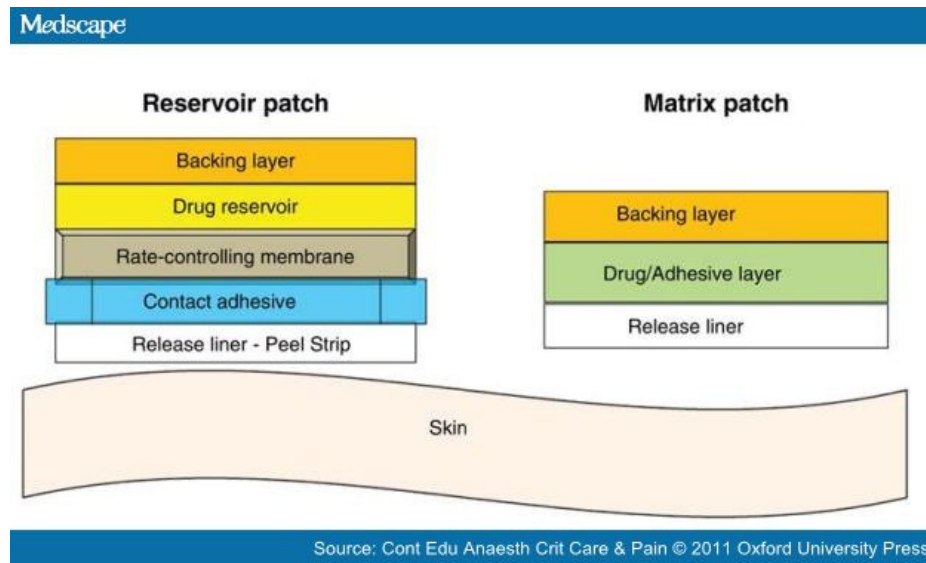
where  $D$  is the diffusion coefficient,  $C_o$  the constant concentration of drug in the patch,  $P$  the partition coefficient between the skin and bathing solution, and  $h$  the thickness of the skin.

Transdermal permeation is improved if the drug has the following properties:

- molecular weight < 500 Da;
- affinity for both lipophilic and hydrophilic phases: extreme partitioning characteristics are not conducive to successful drug delivery via the skin;
- low melting point (affects the release of drug);
- non-ionic;
- high potency (effective at low dosage);
- short half-life.

## Components of a Transdermal Delivery System

The main components of a transdermal drug delivery system (Fig. 1) are:



**Figure 1.**

Components of the reservoir and matrix patches.

- release liner—protects the patch during storage and is removed before its use;
- drug—drug solution in direct contact with the release liner;
- adhesive—adheres the components of the patch together and sticks the patch to the skin;
- membrane—controls the release of the drug from reservoir and multi-layer patches;
- backing laminates—protects the patch from the environment;
- permeation enhancers.

Several different types of transdermal patches are currently available:

1. *Single-layer drug-in-adhesive patch*: the adhesive layer adheres the various layers together and sticks the system to the skin; it is also responsible for releasing the drug.
2. *Multi-layer drug-in-adhesive patch*: both adhesive layers are responsible for release of the drug; one of the layers is for immediate release and the other layer is to control release of the drug from a reservoir.
3. *Reservoir patch*: has a separate drug layer as a liquid compartment, containing a drug solution or suspension, between a backing layer and a rate-controlling membrane; this results in a zero-order rate of release. Reservoir patches should not be cut.
4. *Matrix patch*: has a drug layer of a semi-solid matrix containing a drug solution or suspension dispersed within a polymer pad in direct contact with the skin. The adhesive layer in this patch surrounds the drug layer partially overlaying it.

## Application of Transdermal Delivery Systems in the Management of Pain

### Acute Pain

Transdermal analgesics are now being used in many areas of pain management and by many different patient groups. In the management of acute pain, the pain relief patch has two roles: prevention and treatment. Application of a local anaesthetic patch provides an area of anaesthesia, for example, to prevent the pain of venesection or vaccination.

These patches are particularly useful in paediatric practice. Non-steroidal anti-inflammatory drugs (NSAIDs) are available in patch form to treat acute pain from musculoskeletal injury. Transdermal delivery of opioids has been used for many years, but has not been recommended for use in acute pain due to delayed onset of action and risks of toxicity. The fentanyl patient-controlled transdermal system incorporates advantages of patient-controlled analgesia (PCA) with a transdermal delivery system. It uses an iontophoretic mechanism to speed up drug delivery.

### Chronic Pain

Transdermal analgesics can be useful for the treatment of chronic nociceptive pain. Fentanyl and buprenorphine have been available for many years in patch form. Localized transdermal delivery of drugs may be helpful in the management of chronic neuropathic pain, for example, topical capsaicin and lidocaine patches ([Table 1](#)).

**Table 1. Analgesic patches currently available in the UK. (Adapted from BNF 59)**

| Drug                           | Pharmacological aspect  | Use                                     | Precautions   |
|--------------------------------|---|---|---|
| Diclofenacopolamine (Voltrol®) | NSAID, b.d. patch, worn at the site of injury for up to 2 weeks on unbroken | Acute local pain—sprains and contusions | Same precautions as prescribing any other NSAID drug. Not for children under 15 |

|  |  |   |   |
|--|--|---|---|
|  | skin. 140 mg patch <sup>-1</sup>   |   | yr  |
| Fentanyl                                 | Available as matrix, reservoir patch, or ITS. 3 day matrix patches 12/25/50/75/100 µg h <sup>-1</sup>  | Chronic pain. Acute pain—ITS  | Consider alternative analgesic when patch requirement exceeds 300 µg h <sup>-1</sup> . Elimination <i>T</i> <sub>1/2</sub> 13–22 h  |
| Buprenorphine                            | BuTrans—7 day patch 5/10/20 µg h <sup>-1</sup> . Transtec—3 day patch 35/52.5/70 µg h <sup>-1</sup>  | Chronic pain, primarily osteoarthritic pain   | Up to 3 days for peak action on initial application of 7 day patch and 24 h for 3 day patch. Estimated 30 h for plasma concentration to decrease by 50% after patch removal   |
| EMLA®                                    | Eutectic mixture of 2.5% lidocaine and 2.5% prilocaine—1 g patches. Applied for 1 h before procedure. Can be left in place for 4 h. Up to 2 patches for 3 months–1 yr old, up to 5 patches for 1–6 yr old, and up to 10 for above 7 yr | Before vaccination, venesection, or cannulation. For surface anaesthesia up to 2 h            | Contra-indicated in methaemoglobinaemia. Not for application around eyes, inside ear or mouth. Dose reduction in severe liver and kidney diseases. Do not press the centre of patch when applying as this may displace drug |
| Lidocaine+ Tetracaine plaster (Rapydan®) | Lidocaine 70 mg and Tetracaine 70 mg. To be applied 30 min before procedure. Up to 1–2 plasters below 18 yr and up to 4 plasters above 18  | Surface anaesthesia for needle puncture or superficial surgical procedures                    | Not for children under 3 yr   |
| Tetracaine (Ametop®)                     | 4% tetracaine. Apply 45 min before procedure   | Venepuncture or venous cannulation  | Not in infant below 1 month of age  |
| Lidocaine 5% (Versatis®)                 | Each patch contains 700 mg of lidocaine (50 mg g <sup>-1</sup> ), and measures 10 cm×14 cm. Up to 3 patches can be worn at any one time for up to maximum of 12 h per 24 h period  | Post-herpetic neuralgia. Off-license used in management of peripheral neuropathic pain states | Not for under 18 yr old. Trimmed to match area. Not to be used on broken skin due to risk of overdose. Not to be used with other local anaesthetics   |

## NSAID Patches

The only NSAID patch available in the UK is the Voltarol gel patch containing 1% Diclofenacopolamine. It is licensed for local treatment of pain in epicondylitis and ankle sprain.

Topical NSAIDs are formulated so that they penetrate the subcutaneous tissues and accumulate under the site of application. A recent review<sup>[2]</sup> supports a topical effect and not simply a systemic effect. A reduction in pain scores was demonstrated after 3 h in patients with ankle sprains. As diclofenac first appears in the plasma at a mean of 4.5 h, after topical application, it is thought that the patch must provide analgesia via a local action. After patch removal, due to a local reservoir effect, the plasma diclofenac half-life is ~9–12 h, compared with 1–2 h after oral intake. Systemic transfer after removal of the patch compared with oral forms of diclofenac is only about 2%, so systemic side-effects are very rare. No drug-related gastrointestinal bleeding, ulcers, or cutaneous events, for example, Steven-Johnson syndrome, have been reported during diclofenacopolamine patch use. Most side-effects relate to topical effects: pruritis, erythema, rashes, and rarely allergic dermatitis. A systematic review<sup>[3]</sup> comparing oral diclofenac with topical applications, including the patch form, suggested that diclofenac is superior to placebo in reducing the pain in osteoarthritis of the knee and sports-related soft tissue injuries. It is at least as effective as oral diclofenac and some studies suggest that it may be superior.

## Opioid Patches

The  $\mu$ -agonist fentanyl and the partial  $\mu$ -agonist buprenorphine both have high lipid solubility and a low molecular weight making them well suited to being delivered transdermally.

**Fentanyl Patches** Transdermal delivery of fentanyl is licensed for palliation of malignant and non-cancer pain. Manufacturers have used the matrix and reservoir design for drug delivery, for example, 'Fentalis' and 'Tilofyl' are reservoir patches and 'Mezolar' and 'Osmanil' use the matrix design. Matrifen has a silicone drug containing matrix with a rate-controlling membrane. The proprietary Durogesic D-Trans has an adhesive matrix containing dissolved fentanyl.

Each patch is designed to maintain a constant plasma fentanyl concentration over a 72 h application with maximum plasma concentrations between 12 and 24 h. Blood flow and anatomical site of application does not affect the rate of drug delivery. Exposure to a heat source or an increase in body temperature can increase fentanyl delivery by up to one-third. Owing to the slow increase in initial fentanyl plasma concentrations, it is important that evaluation of analgesic efficacy should occur after 24 h; other analgesia may be required during this initial period. The delay is due to the formation of a fentanyl depot within the skin layers before the drug entering the systemic circulation. Conversely, after patch removal, fentanyl is eliminated slowly due to the depot collection. Elimination can be delayed even further by the co-administration of CYP3A4 inhibitors, for example, ketoconazole, clarithromycin, verapamil, diltiazem, and amiodarone.

Patches are prescribed based on the number of micrograms per hour of drug released. The MHRA<sup>[4]</sup> has advised that fentanyl patches should only to be used in patients who have previously tolerated opioids due to the risk of ventilatory depression in opioid naïve patients. [Table 2](#) illustrates dose equivalence. Multiple case reports have been submitted to the MHRA of unintentional overdose due to dosing errors, accidental exposure, and exposure of a patch to a heat source. The MHRA recommend that physicians must fully inform patients or caregivers of their safe use and potential side-effects.

A case review of eight deaths in the USA during 2006, caused by overdoses of transdermal fentanyl, has highlighted the narrow therapeutic/toxic window.<sup>[5]</sup>

In an open-label study,<sup>[6]</sup> transdermal fentanyl significantly improved pain control and quality of life in patients with chronic pain related to osteo or rheumatoid arthritis, when replacing simple analgesics and weak opioids. Non-blinded randomized trials<sup>[7]</sup> suggest that transdermal fentanyl is an effective alternative to oral morphine in the management of

cancer pain. In this group, significantly more patients expressed a preference for transdermal delivery in a cross-over trial.

**Buprenorphine Patches** Buprenorphine is a strong opioid derived from the baine. Two forms of patch are available: the 96 h Transtec® patch and the 7 day Butrans® patch, both use a matrix design.

Buprenorphine patches have been shown to be useful in both chronic cancer and non-cancer pain. A post-marketing surveillance study<sup>[8]</sup> in 13 179 patients with moderate to severe cancer and non-cancer pain showed that Transtec® provided effective and sustained pain relief, only 6% patients changed to alternative analgesics. A retrospective cohort study<sup>[9]</sup> of the 7 day buprenorphine patch in general practice demonstrated improved patient compliance with treatment for 6 and 12 months, when compared with codeine, dihydrocodeine, and tramadol; but there was increased nausea, vomiting, dizziness, and constipation associated with the use of the patch (Table 2).

**Table 2. Dose equivalence of opioid patches**

| Patch formulation | Delivery rate ( $\mu\text{g h}^{-1}$ ) | S.C. morphine [ $\text{mg (24 h)}^{-1}$ ] | Oral morphine [ $\text{mg (24 h)}^{-1}$ ] | Oral oxycodone [ $\text{mg (24 h)}^{-1}$ ] |
|-------------------|--|---|---|--|
| Fentanyl 12       | 12                                     | 10–20                                     | 20–60                                     | 15–40                                      |
| Fentanyl 25       | 25                                     | 30–40                                     | 60–100                                    | 40–70                                      |
| Fentanyl 50       | 50                                     | 60–80                                     | 120–200                                   | 80–140                                     |
| Fentanyl 75       | 75                                     | 90–120                                    | 180–300                                   | 120–200                                    |
| Fentanyl 100      | 100                                    | 120–160                                   | 240–400                                   | 180–270                                    |
| Buprenorphine     | 5                                      | 9–13                                      | 5–10                                      |  |
| Buprenorphine     | 10                                     | 18–26                                     | 10–20                                     |  |
| Buprenorphine     | 20                                     | 36–53                                     | 25–40                                     |  |

**Fentanyl HCl Iontophoretic Transdermal System** The fentanyl HCl iontophoretic transdermal system (Fentanyl ITS) is the only transdermal opioid that has a role in the management of acute pain; it is licensed for patient-controlled management of moderate-to-severe postoperative pain in the hospital environment.

The system consists of a credit-card-sized patch that is applied to the patient's upper outer arm or chest. When the on-demand button is pressed twice within 3 s, a pre-programmed dose of 40  $\mu\text{g}$  of fentanyl is delivered transdermally over a 10 min period. A maximum of six doses may be delivered per hour, and this cannot be changed. A small LED indicates when a dose is being delivered. The system can also be interrogated about how many doses have been given. Each system lasts for 24 h or 80 doses and it is then discarded.

The active delivery of fentanyl means that the mean time to peak fentanyl serum concentration is greatly reduced: being

only 39 min in one study. After discontinuation of fentanyl PCA, plasma concentrations decrease at a rate similar to that following i.v. administration, suggesting that there is no development of a skin depot.

The fentanyl ITS system has been shown to be superior to placebo in randomized controlled trials<sup>[10]</sup> for treatment of moderate-to-severe pain after orthopaedic, abdominal, and thoracic surgery. An active comparator phase III trial found it to provide equivalent analgesia to standard i.v. PCA morphine. The most frequent adverse events were those typical of opioid therapy, for example, nausea, vomiting, and pruritis. To date, there have been no reports of ventilatory depression. Application site reactions occurred in 13% of patients, the majority were mild-to-moderate erythema, vesicles, and itching.

**Local Anaesthetic Patches** Topical local anaesthetics have been used to reduce the pain of venepuncture. More recently, a topical lidocaine patch, Versatis (5%), has been used for the symptomatic relief of neuropathic pain associated with post-herpetic neuralgia. The patch has a direct local action with limited systemic effects. It is well tolerated, with application site reactions being the most commonly reported adverse effect. Systemic absorption is directly related to the duration of application and area of skin contact; it is about 40 times lower than toxic levels in adults.

There are only limited data supporting the use of lidocaine 5% patch in post-herpetic neuralgia. Small randomized controlled trials<sup>[11]</sup> have confirmed that Versatis produced superior pain relief than placebo in short-term studies. A Cochrane review<sup>[12]</sup> concluded that 'there is insufficient evidence to recommend topical lidocaine as a first line therapy in post herpetic neuralgia with allodynia'. Further studies are awaited.

## The Future of Transdermal Drug Delivery

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Transdermal delivery of analgesics is likely to continue to increase in popularity as there are further improvements in design. Research is being performed to increase safety and efficacy. To improve practical matters such as the experience for the wearer of the patch, and also to provide more precise drug delivery associated with increased duration of action.

Other potential improvements include improved transdermal technology that utilizes mechanical energy to increase drug flux across the skin either by altering the skin barrier or increasing the energy of the drug molecules. After the successful design of patches using iontophoresis, various modes of 'active' transdermal technologies are being investigated for different drugs. These include electroporation (short electrical pulses of high voltage to create transient aqueous pores in the skin), sonophoresis (uses low-frequency ultrasonic energy to disrupt the stratum corneum), and thermal energy (uses heat to make the skin more permeable and to increase the energy of drug molecules). Magnetic energy, magnetophoresis, has been investigated as a means to increase drug flux across the skin.

Many analgesics in patch formulation are at different trial stages, with several showing promise. Capsaicin 8% (Qutenza™), a 1 h patch, has been tested and approved by the FDA; it appears to show a reduction in pain scores in post-herpetic neuralgia and HIV neuropathy. A bupivacaine patch (Eladur™), with continuous delivery for up to 3 days from a single application, promises longer duration of action, faster onset, and potentially deeper tissue penetration than the lidocaine patch. It may be useful in localized neuropathic pain. Sufentanil and oxycodone patches are in trial phase and may be a useful addition to the formulary.

The transdermal patch may be an underutilized tool for management of acute and chronic pain. With improved delivery and a wider range of analgesics, we expect the popularity and applicability of this modality to deliver drugs to increase.

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## Sidebar

## Key Points

- Transdermal drug delivery offers pharmacokinetic and practical advantages over the oral or parenteral routes for some patients.
- Patch design has important implications, for example, reservoir patches should never be cut whereas matrix patches can be trimmed.
- Topical diclofenac is at least as effective as the oral form; it may be superior.
- Development of a local subcutaneous drug reservoir beneath the patch means that buprenorphine and fentanyl patches require 24–72 h before the peak effect is achieved and there is delayed elimination after patch removal.
- New technology to actively drive drug molecules through the transdermal barrier may reduce time to onset and allow patch delivery to be useful in the management of acute pain.

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