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TRANSDERMAL DRUG DELIVERY SYSTEMS

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TRANSDERMAL DRUG DELIVERY SYSTEMS

INTRODUCTION

As anaesthetists we are mostly familiar with the classic methods of delivering a drug into the body, i.e. the IV, IM, PO routes, as well as inhalational delivery of the volatiles. However, we need to be aware of the new methods of drug delivery that have been developed and that are set to revolutionise our understanding of pharmacology.

Over the past three decades a new era in science and technology has evolved in pharmaceutical research that has focused on the development of novel drug delivery systems. Changing a drug from its original form to a novel drug delivery system may assist in improving the efficacy and safety of the drug and may also contribute to greater patient compliance. The method of administering a drug can have significant effect on its efficacy. Therefore, it is essential to give, "the right drug, at the right dose, at the right time, via the right route".

HISTORY ¹

Since time immemorial, people have been applying medication on their skin in an attempt to heal ailments. These applications were intended to produce a local and topical effect. Using adhesive skin patches to deliver drugs systemically is a relatively new phenomenon.

The scopolamine patch for motion sickness was the first adhesive transdermal patch and was approved by the FDA in 1979. Nitro-glycerine patches were approved in 1981. Nicotine patches were introduced in 1991. Transdermal drug delivery systems are now an important area of research as they have pharmacological advantages over the oral route and have been shown to have improved patient compliance.

ACTIVE INGREDIENT	INDICATION
Buprenorphine	Analgesia
Clonidine	Hypertension
Oestradiol and progesterone	Hormone replacement
Ethinylestradiol, Norelgestromin	Contraception
Fentanyl	Analgesia
Glyceryl trinitrate	Angina
Hyoscine	Motion sickness
Lisuride	Parkinson's disease/restless legs syndrome
Nicotine	Smoking cessation
Testosterone	Hypogonadism

Table 1 Transdermal patches licenced in the UK

SKIN STRUCTURE 2,3,10

The skin is largest organ in the body. It protects against the influx of toxins and the efflux of water and it is largely impermeable to the penetration of foreign molecules.

Skin serves as the point of administration for systemically active drugs. The topically applied drug will first be absorbed into the systemic circulation and then transported to target tissues.

There are three layers that make up skin. Epidermis, dermis and subcutaneous tissue. The epidermis, in particular the stratum corneum is the major barrier to drug absorption. With respect to drug delivery, molecules must penetrate the stratum corneum, the viable epidermis, the papillary dermis and the capillary walls into the blood stream or lymph channels, whereupon they are removed from the skin by flow of blood or lymph.

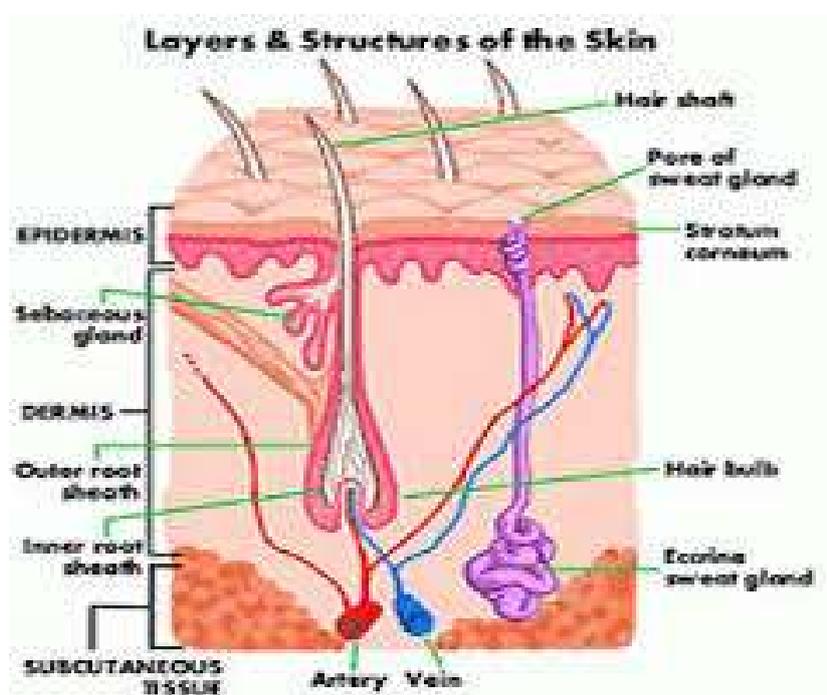


Figure 1: Structure of the skin

Routes of penetration⁵

The following routes are observed in transportation of the drug through the skin barrier

- Across the intact horny layer
- Through the hair follicles with the associated sebaceous glands, or
- Via the sweat glands

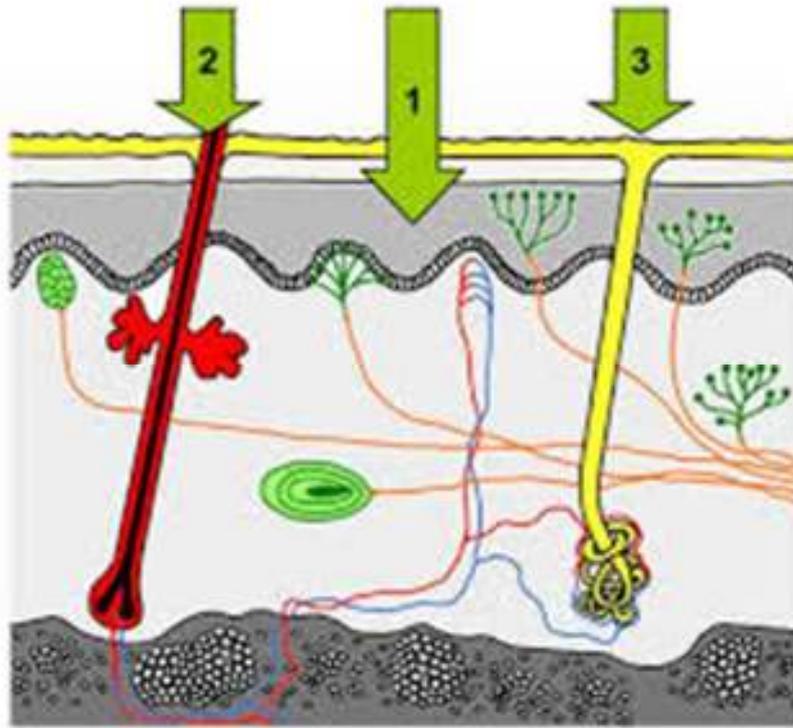


Figure 2: Possible routes of penetration

Factors affecting Transdermal Permeability

- a. Physico-chemical Properties of the Penetrant Molecules
 - Penetrant concentration
 - Partition coefficient
 - pH conditions
- b. Physico-Chemical Properties of Drug Delivery Systems
 - Release Characteristic
 - Enhancement of transdermal permeation
- c. Physiological and Pathological Conditions of the skin
 - Reservoir effect of horny skin
 - Lipid film
 - Pathological injuries to the skin
 - Skin temperature
 - Regional variations skin hydration
 - Cutaneous self-metabolism

PHARMACOKINETICS OF TRANSDERMAL DRUG DELIVERY ^{10,17}

- The drug is stored in the TDDS as either a reservoir or impregnated into the fabric of the patch.
- Once the TDDS is applied to the skin, a concentration gradient is established and the drug begins to move down the gradient.
- A second drug reservoir is established in the stratum corneum.
- Once the drug moves further into the skin, it is absorbed into the local capillary vasculature and is then transported into the systemic circulation.
- Because of this absorption process, there is a delay between applying the patch and developing a minimum effective concentration (MEC).
- The time to reach steady-state plasma concentrations differs greatly between drugs and may only be achieved after two or three patch applications.
- Steady state is then maintained for the duration of time that the patch is applied.
- The continuous drug delivery provided by TDDS is associated with better patient compliance.
- Once the patches are removed, the concentration of the drug decreases gradually.
- The rate of decline depends on the drug's context sensitive half-time and whether a reservoir has formed in the skin.

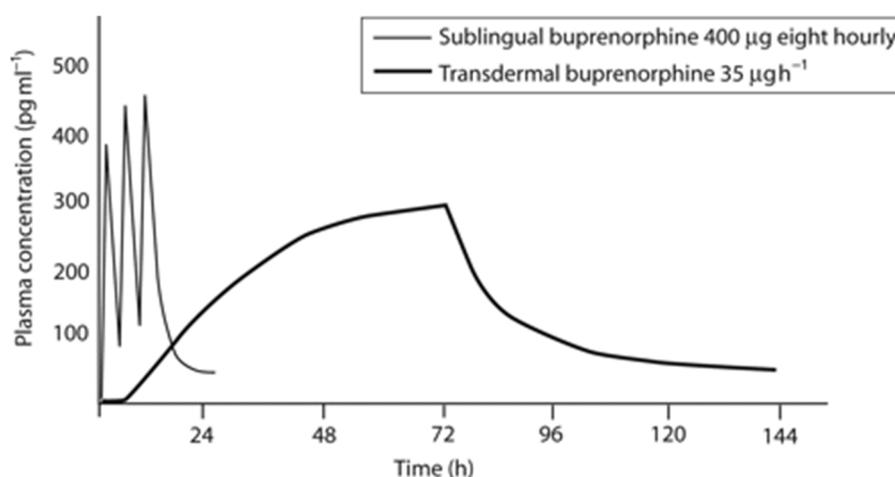


Figure 3: Comparison of plasma concentrations of buprenorphine after single application of 35 ug h⁻¹ patch (removed after 72hr) and sublingual dosing of 400ug of buprenorphine, eight hourly

Ideal properties of TDDS

- The ideal properties of a TDDS are:
 - Optimum partition coefficient required for the therapeutic actin of drug
 - Shelf life up to 2 years
 - Low melting point of the drug is desired which is <200 C
 - Patch size should be <40cm
 - The pH of the saturated solution should be between 5-9

ADVANTAGES OF TDDS ^{8,9}

- The avoidance of first pass metabolism of drugs
- No interference with gastric and intestinal fluids
- Due to the steady infusion of the drug over a long period the adverse effects associated with intermittent dosing are avoided
- There is increased patient compliance due to the painless, non-invasive and simple application
- Able to achieve more stable and controlled blood levels for a longer period
- Characteristics are comparable to intravenous infusions
- This route is suitable for the administration of drugs that have a short half life, narrow therapeutic window and poor oral bioavailability
- Removing the patch terminates the drug administration

LIMITATIONS OF TDDS

- Local irritation may occur at the site of application
- Drugs that have a large molecular size make absorption difficult. Ideally the drug molecule should be below 80-100 Daltons.
- Hydrophilic drugs are not suitable for transdermal delivery
- The barrier function of the skin changes and is dependent on patient profile
- TDDS cannot achieve high drug levels in blood/plasma

TYPES OF TDDS ^{13,14}

The two types of transdermal patches that are available are:

- a. The reservoir or membrane-controlled system
- b. The matrix system

The Reservoir System

- The drug is stored in a reservoir enclosed on one side with an impermeable backing.
- On the other side is an adhesive surface for application on the skin.
- Some patches contain the drug dissolved in a liquid or gel. This allows for simplified formulations and the use of liquid chemical enhancers such as ethanol
- They are typically composed of four layers:
 - i) Impermeable backing membrane
 - ii) The drug reservoir itself
 - iii) A semi-permeable membrane (may act as a rate-limiting barrier)
 - iv) Adhesive layer
- Reservoir patches give tighter control of delivery rates but can have an initial burst of drug release.
- If the membrane is damaged, there is also a risk of sudden release of drug into the skin and over-dose as potentially, a larger area of skin is exposed for drug absorption.

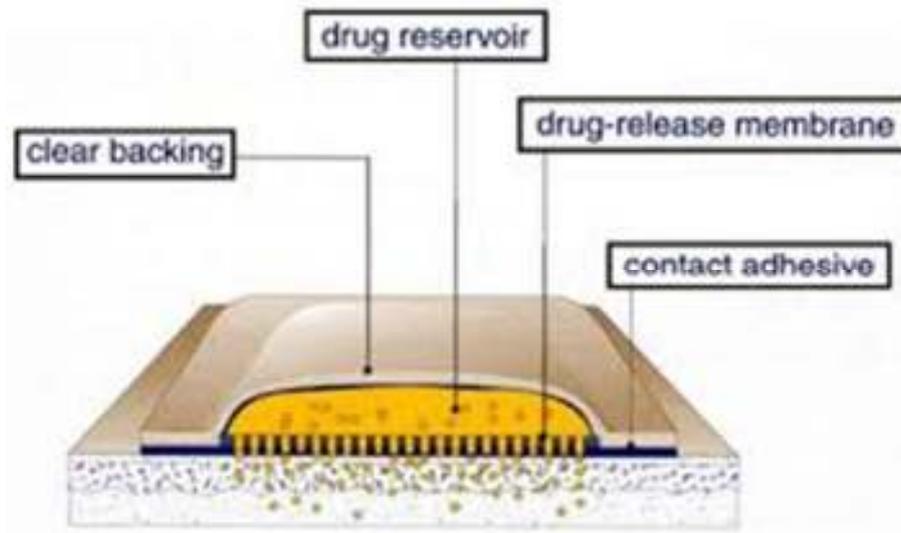


Figure 4: Transdermal reservoir patch

The Matrix System

- The matrix patch incorporates the drug into an adhesive polymer matrix, from which the drug is continuously released into the skin.
- The dose of the drug depends on the amount of drug held in the matrix and the area of the patch applied to the skin.
- In a matrix patch, the active ingredient is distributed evenly throughout the patch.
- One half of a patch will have half the original surface area and deliver half the original dose per hour.
- The matrix patch carries less risk of accidental overdose and offers less potential for abuse than the reservoir system

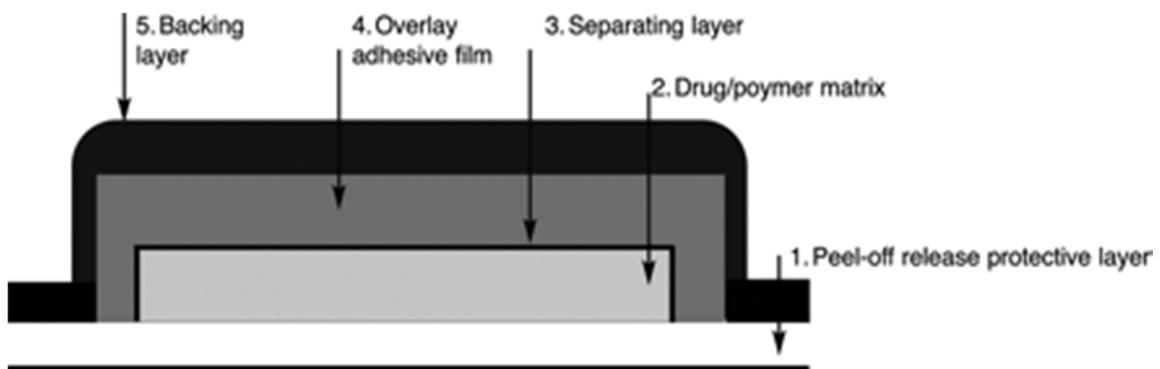


Figure 5: Cross section through a matrix patch

IMPROVING TRANSDERMAL DRUG DELIVERY ^{17, 18}

- The limitations on drug delivery that are caused by the barrier function of the skin have led to a search for methods of improving delivery of drugs through the stratum corneum.
- These methods can be in the form of either physical or chemical delivery systems, or formulations which improve transdermal delivery.
- Chemical methods include adding ethanol or propylene glycol to enhance solubility.

Physical methods

i. Phonophoresis(sonophoresis)

- Use of therapeutic ultrasound to increase percutaneous drug absorption.
- To be effective, medication should penetrate below stratum corneum to reach the capillary network.
- Drug is applied at target site and massaged with a therapeutic ultrasound applicator, either via continuous or pulsed mode. Continuous mode causes an increase of temperature in the tissues, while pulsed causes cavitation, acoustic streaming, micro streaming increased skin pore size and numbers and increased intercellular spaces. However the effect is greater with pulsed probably due to the cavitation effect
- Low frequencies can deliver macromolecules such as liposomes and nanoparticles (FDA approved).

ii. Magnetophoresis

- Application of a magnetic field enhances permeability.
- It is a patch system, which consists of magnets arranged in parallel on adhesive backing membrane. Octanol/water partition coefficient of the drug increases when exposed to the magnetic field. Permeability increases ~3 times more.
- Enhancers that are used are menthol, sodium lauryl sulphate acts on lipoidal areas whereas DMSO and urea act on the keratinocytes. When added, permeability increases ~4-7 times more.

iii. Electroporation

- Used short duration (fraction of a second) high voltage pulses. Then time is allowed for skin to depolarize, therefore there is no disruption to the current flow or drug diffusion. - This creates pores through the subcutaneous lipids and increases delivery X2-8 more.

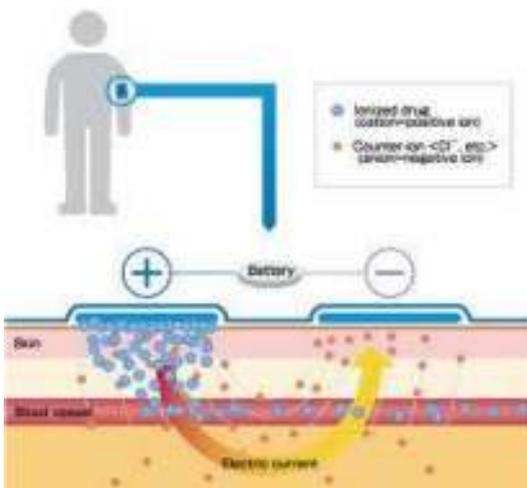
iv. Microporation

- Minimally invasive? But can increase the delivery of macromolecules -
- There are 3 types:
 - Micro needle technology: needles give controlled release. Can be incorporated with iontophoresis or electroporation. Also can use drug carriers such as lipid vesicles, macro and nanoparticles.
 - Thermal micro-incorporation
 - Laser ablation – this is a novel way which creates well-defined conduits.

v. Iontophoresis or electromotive drug administration (EMDA) 8

- Injection without a needle
- “Permeation of ionized drug molecules across biological membranes under the influence of electrical current”

- Uses a constant low-voltage direct electrical current as a driving force for permeation of ionic and non-ionic medications. Non-invasive method of propelling high concentrations of a charged substance (medication or bio-active agent) through the skin by repulsive
Electromotive force using a small electrical charge applied to an iontophoretic chamber containing a similarly charged active agent in a vehicle e.g. saline.
- There is a positively charged chamber (anode) which will repel a positively charged chemical, and a cathode chamber (on a different part of the skin) which will repel a negatively charged chemical into the skin
- This temporarily alters the barrier properties of the skin, thereby possibly improving penetration of drugs such as proteins, peptides and other macromolecules, as well as high molecular weight molecules with controlled input kinetics and minimum inter-subject variability.
- Current used is very small $< \text{or } = 0,5 \text{ mA/cm}^2$. Within this electric field electro-migration and –osmosis are the dominant forces in transport of a specific dose of drug. Placing an electrode of the same polarity as the drug on an opposing area, drives the ionically charged drugs through the skin, measured in units of chemical flux, commonly $\mu\text{mol/cm}^2\text{h}$.
- The drug is driven into the skin by electrostatic repulsion and electro-osmosis. Electro osmosis is the result of the skin supporting a net negative charge at physiological pH.



- Reverse iontophoresis:
 - o Process by which molecules are removed from the body.
 - o The negative charge of the skin at buffered pH causes it to be perm selective to cations, causing solvent flow towards the anode of neutral molecules e.g. glucose. GlucoWatch is a device which uses this technology to test serum glucose.
- Iontophoresis is used for:
 - o NSAID delivery by physiotherapists to treat plantar fasciitis, bursitis etc.
 - o Hyperhidrosis (see diagram above). Solution chosen is usually tap water, but better results can be obtained using glycopyrronium bromide, a cholinergic inhibitor.
 - o Pilocarpine iontophoresis is often used to stimulate sweat secretion, as part of cystic fibrosis diagnosis.

Formulations which improve transdermal delivery^{11, 12}

i. Liposomes

- Lipids (liposomes) and surfactants (niosomes) can be formed into vesicles which easily penetrate the skin.
- Size of liposome is important for skin penetration 600nm crosses easily
- They are microscopic vesicles that contain amphipathic phospholipids arranged in one or more concentric bilayers enclosing an equal number of aqueous compartments. - May serve as local depots (reservoir effect) for sustained drug release.
- They decrease systemic absorption or toxicity and act as a controlled transdermal delivery system.
- There are special vesicular systems that can deliver ionic molecules and polypeptides across the skin into deeper layers with better stability and efficiency.

1. Ethosomes

- Permeation enhancer
- Cause fluidization of lipids in stratum corneum.
- Composed of phospholipids, water and ethanol

2. Transfersomes

- Consist of ultra-deformable liposomes with elasticity and deformability in the lipid bilayer.
- Rapidly penetrate the intracellular lipids of the subcutaneous layers.

3. Niosomes

- Can be formed from a diverse array of amphiphiles.
- The non-ionic surfactant vesicles are similar to liposomes with unilamellar or multilamellar structures
- Enhance skin permeation of drugs by disrupting the membrane properties of subcutaneous tissues and by directly fusing into the upper layer of skin.
- Have application in topical and systemic products and have been used to encapsulate lignocaine.
- Short shelf-life because of aggregation, fusion, leaking or hydrolysis of entrapped drugs.

4. Proniosomes

- Forms part of a delivery system that produces an isotonic multilamellar niosomal suspension when hydrated immediately before use.
- This aids storage and transport.
- The non-ionic surfactant components used in these systems are Sorbian esters, cholesterol and phospholipids with enhanced morphology, particle size and drug release performance.
- Pharmacosomes, a colloidal dispersion of drugs, are another type of carrier which is covalently linked to phospholipids.

ii Microspheres

- There are various drug delivery systems to deliver a drug to a target site in a sustained, controlled released fashion
- One of the methods is using microspheres as drug carriers.
- Microspheres are spherical in shape and vary from 1-300um
- They are made from albumin, starch, gelatin, dextran, polypropylene etc.
- Advantages of these microspheres are that they can be injected or ingested and that they produce sustained release action and site specific delivery.

iii Nanoparticles

- Are sub-micron sized particles 10-200nm in size
- They are widely used as carriers due to their stability and long term storage.
- They can encapsulate or adsorb the drug and help to protect it from chemical and enzymatic degradation.

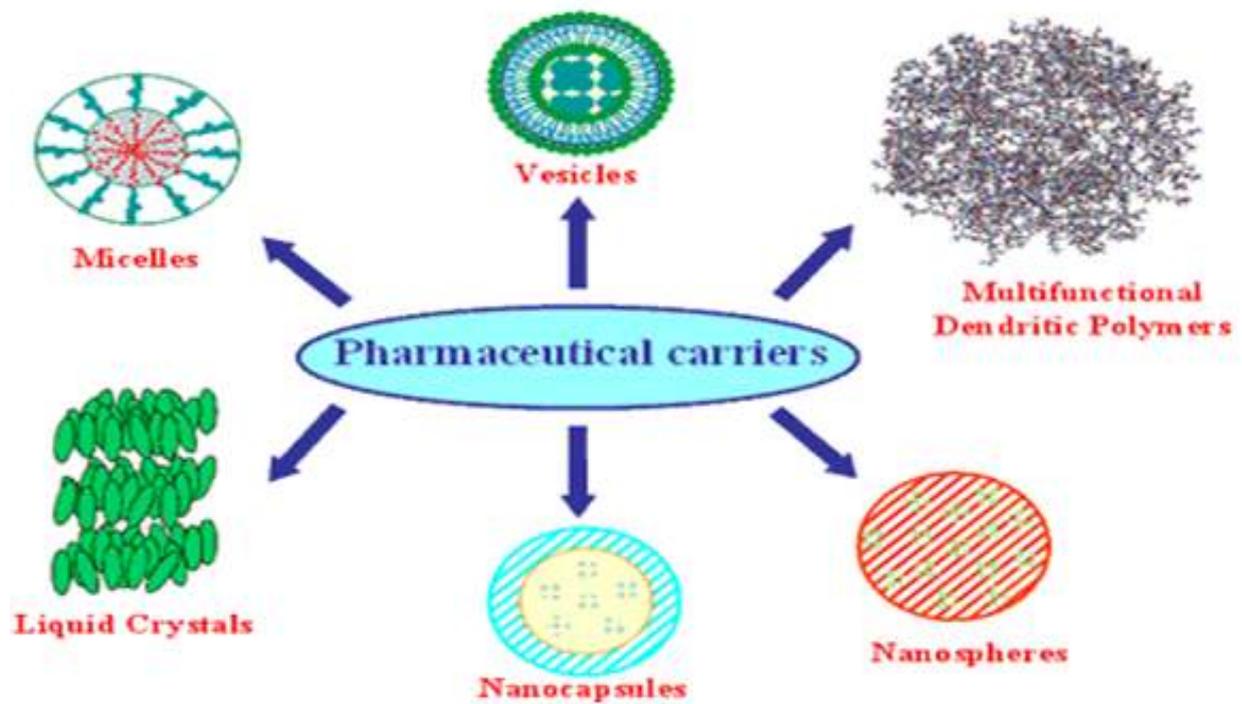


Figure 6: Types of drug carriers

OPIOID TRANSDERMAL DRUG DELIVERY SYSTEMS

- The side effects from opioid administration, are a result of the peaks and troughs that come from intermittent dosing. Transdermal delivery avoids this.
- patients are more compliant and there is a decreased in the dosing intervals

Fentanyl Transdermal Delivery

- Fentanyl is soluble in both lipid and water. It is therefore the ideal agent for transdermal delivery.
- The first Fentanyl patch was the Durogesic patch. This was a reservoir design. It is now being replaced by a matrix patch – DTrans.
- DTrans is smaller and thinner than Durogesic and there is less risk of accidental overdose from membrane damage.+
- Fentanyl patches deliver fentanyl at four constant rates: 25, 50, 75, and 100 mg h⁻¹ for a period of 72 h. After the first application, a depot of fentanyl forms in the upper skin layers and serum fentanyl concentrations increase gradually, generally levelling off between 12 and 24 h. The steady-state serum concentration is reached after 24 h and maintained as long as the patch is renewed.
- However, variations have been found in serum fentanyl concentration during the 72 h period; concentrations tend to be higher in the first 24 h and decrease on the second and third day due to the decreasing concentration gradient between patch and skin. Fentanyl delivery is not affected by local blood supply, but an increase in body temperature can increase absorption rate by about 30 %.
- Fentanyl is metabolized by the P450 cytochrome enzyme system to inactive metabolites. Drugs that enhance or inhibit cytochrome function will affect metabolism, for example, cimetidine and isoniazid. The elimination half-life after patch removal is 13–22 h, this is probably due to slow release of fentanyl from the skin depot.
- Another analgesic is necessary in the first 12hrs because of the slow increase in plasma concentration when fentanyl is first applied. Replacement opioid therapy should be started gradually after patch removal, and those patients who have severe side-effects should be monitored for 24 h. Dosage adjustments should not be made at <72 h intervals.



Figure 7: Fentanyl transdermal patch

Fentanyl patient controlled transdermal system

- The fentanyl patient-controlled transdermal system (PCTS) is approximately the size of a credit card and is worn on the upper arm or chest.
- Iontophoresis is utilized to deliver fixed drug boluses. There is no background infusion, and passive absorption from the system is negligible. Plasma fentanyl concentrations decline rapidly after patch removal. Fentanyl PCTS 40 mg has been shown to be superior to placebo and equivalent to i.v. morphine PCA for the treatment of acute postoperative pain. The fentanyl PCTS has the advantage of being less cumbersome than i.v. systems but a potential disadvantage is the preprogrammed fixed dose; although this eliminates the possibility of programming errors, it means that the device will be unsuitable for those patients with higher opioid requirements.

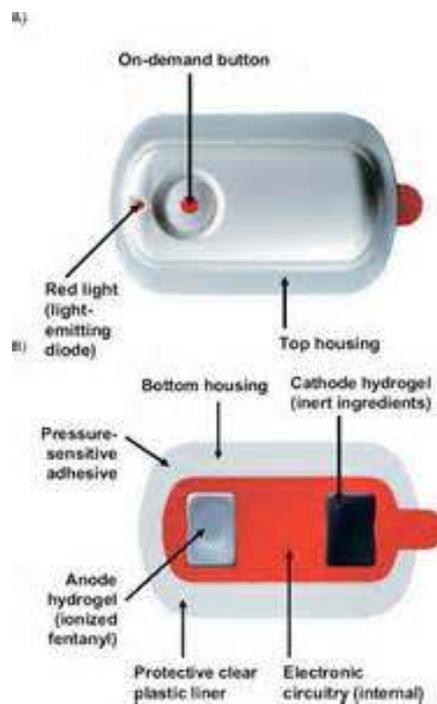
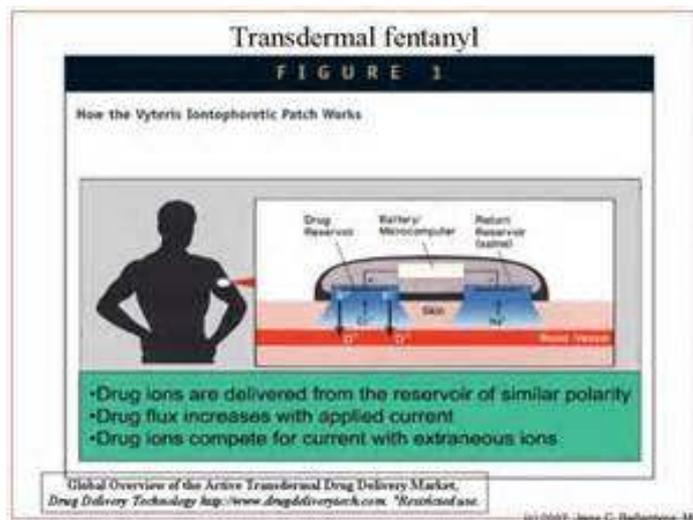


Figure 8: Fentanyl patient controlled transdermal system

Buprenorphine TDDS

- Buprenorphine is a partial agonist at μ -receptors; it is 60 times more potent than morphine. A ceiling effect is reached at doses of .16 mg day⁻¹. This does not happen in clinical practice as the patches are designed to deliver 35, 52.5, or 70 mg h⁻¹ and the maximum dose is 3.36 mg day⁻¹ (two 70 mg h⁻¹ patches).

- Effective plasma concentrations are reached within 12–24 h of patch application. As with fentanyl, metabolism is by the CYP 3A4 system, but offset after patch removal is slower due to the high affinity of buprenorphine for opioid receptors. Patients with severe side-effects should be observed for 30 h after removal of the patch. A recent development is the release of a 7 day buprenorphine patch. This buprenorphine patch is a matrix system, available in three sizes, delivering 5, 10, or 20 mg h⁻¹ of buprenorphine over 7 days, and licensed for the treatment of moderate to severe pain.



Figure 9: Buprenorphine patches

Clinical efficacy of opioid TDDS

- Opioid TDDS have proven to be efficacious in the long-term management of chronic malignant and non-malignant pain.

- Transdermal opioids have proven helpful in managing patients suffering with chronic low back pain and chronic musculoskeletal disorders. In both groups, patient satisfaction is greater with preference for transdermal drug delivery as this is associated with less side-effects (e.g. constipation) and is more convenient. Improvements in measures of quality of life have also been reported in cancer pain patients receiving opioid TDDS.

Unfortunately, transdermal patches are open to abuse, sometimes with fatal consequences. There are reports of fentanyl being extracted from patches for intravenous injection. This

more common with the reservoir patch. Respiratory depression and cognitive dysfunction are important side-effects of opioid patches. Patients should be clearly educated about the potential adverse effects and cautioned against using alcohol or other sedative medication concurrently with opioid patches. Because of the unique pharmacokinetics of the TDDS systems, the depressive effects are not immediately reversed by patch removal; in emergency situations, i.v. naloxone may be required to reverse this sedative effect. Cognitive dysfunction can present with a wide range of neuropsychological side-effects, including mental dullness, euphoria, and reduced attention, concentration, and memory. Ability to drive motor vehicles has been investigated; there was no significant difference in performance measures between patients with fentanyl patches and controls.

Unintended exposure is also a real but rare complication. Children can be exposed to the drug by patches being inadvertently transferred onto the child after hugging an adult with a patch on. It is very important to avoid children coming into contact with opioid patches; fatal consequences have been reported.

Perioperative pain management of patients using opioid patches¹⁰

Guidelines for the management of acute pain in patients on long term opioid therapy

- † Involve the hospital acute pain team early.
- † Cover the patient's baseline opioid requirement. One can either leave the TDDS on or to change to an equivalent opioid dose via intravenous infusion. Where possible, continue the usual TDDS regimen to cover the chronic pain element.
- † Use a .multi-modal approach. Regional blocks, NSAIDS, Acetaminophen
- † Note that higher doses of opioids will be required for post op analgesia
- † Stopping the patient's usual opioid dose will lead to withdrawal symptoms.
- † The opioid dose given via TDDS must never be adjusted in an attempt to control the acute pain.
- † Ensure that everyone involved in the care of the patient is aware of the TDDS and the strategy for pain management.

CONCLUSION

Transdermal drug delivery addresses the low bioavailability of oral drugs.

Eliminates the pain and inconvenience of injections and addresses the limited release options of both.

REFERENCES

1. Guy RH, Hadgraft J, editors. New York: Marcel Dekker; 2003. Transdermal Drug Delivery.
2. Williams A. London: Pharmaceutical Press; 2003. Transdermal and Topical Drug Delivery.
3. Prausnitz MR, Mitragotri S, Langer R. Current status and future potential of transdermal drug delivery. *Nat Rev Drug Discov*. 2004;3:115–124. [[PubMed](#)]
4. Bronaugh RL, Maibach HI, editors. Edn. 4th. New York: Marcel Dekker; 2005. Percutaneous Absorption.
5. Sharma, Saini, Rana Transdermal Drug Delivery System : A Review , *International Journal of Research in Pharmaceutical and Biomedical Sciences*, 2013
6. Prausnitz MA, Langer Transdermal Drug Delivery, *Nat Biotechnol* 2008 26 1261-126
7. Bheemidi , Truckovela, Varanasi, An imperative note on Novel Drug Delivery Systems, 2011
8. Mayes S, Ferrone M. Fentanyl HCl patient-controlled iontophoretic transdermal system for the management of acute postoperative pain. *Ann Pharmacother*. 2006;40:2178–2186. [[PubMed](#)]
9. Sieg A, Guy RH, Delgado-Charro MB. Noninvasive and minimally invasive methods for transdermal glucose monitoring. *Diabetes Technol Ther*. 2005;7:174–197. [[PubMed](#)]
10. Margetts L, Sawyer R Transdermal Drug Delivery : Principles and Opioid Therapy, *Continuing Education in Anaesthesia* 2007
11. Williams AC, Barry BW. Penetration enhancers. *Adv Drug Deliv Rev*. 2004;56:603–618. [[PubMed](#)]
12. Smith EW, Maibach HI, editors. Boca Raton, FL: Taylor and Francis Group; 2006. Percutaneous Penetration Enhancers.
13. Karande P, Jain A, Ergun K, Kispersky V, Mitragotri S. Design principles of chemical penetration enhancers for transdermal drug delivery. *Proc Natl Acad Sci U S A*. 2005;102:4688–4693. [[PMC free article](#)] [[PubMed](#)]
14. Kogan A, Garti N. Microemulsions as transdermal drug delivery vehicles. *Adv Colloid Interface Sci*. 2006;123–126:369–385. [[PubMed](#)]
15. Touitou E, Godin B. Enhancement in Drug Delivery. In: Touitou E, Barry B, editors. Boca Raton, FL: CRC Press; 2007. pp. 255–278.
16. Sloan KB, Wasdo SC, Rautio J. Design for optimized topical delivery: Prodrugs and a paradigm change. *Pharm Res*. 2006;23:2729–2747. [[PubMed](#)]
17. Banga AK. London: Taylor & Francis; 1998. Electrically-Assisted Transdermal and Topical Drug Delivery.
18. Kalia YN, Naik A, Garrison J, Guy RH. Iontophoretic drug delivery. *Adv Drug Deliv Rev*. 2004;56:619–658.