Transdermal Drug Delivery Systems (TDDS)

TDDS facilitate the passage of therapeutic quantities of drug substances through the skin into the general circulation for their systemic effects, with the skin not being the target organ.

Advantages of TDDS

- They can avoid gastrointestinal drug absorption problems caused by GIT pH, enzymes and drug interaction with food, drink or with other orally administered drugs.
- They avoid the first-pass effect responsible for metabolism and deactivation of drug by liver enzymes.

- They can substitute for oral administration of drugs when that route is unsuitable as in cases of vomiting and or diarrhoea.
- They provide extended therapy with a single application, thereby improving patient compliance over other dosage forms requiring more frequent dose administration.
- TDDS are non-invasive, avoiding the inconvenience of parenteral therapy.
- Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.
- Ease of rapid identification of the medication in emergencies e.g. unconscious or comatose patient due to the identifying-markings on the TDDS.

Disadvantages

- Not all drugs are suitable candidates for TDDS due to the natural limit of drug entry imposed by the skin impermeability.
- Some patients may develop contact dermatitis at the application site, requiring the discontinuation of therapy.

There are certain parameters that can be used to predict the feasibility of an active drug ingredient for transdermal administration. These include:

1. Log *P*, ideally the log partition coefficient of the drug should be in the range of 1-3.
2. Molecular weight (MW), ideally the molecular weight of the drug should be less than 500 Dalton.
3. Aqueous solubility, ideally the aqueous solubility of the drug should be equal or greater than 1 mg/mL.
4. Melting point of the permeant should be less than 200 °C.
5. The effective daily dose of the drug should be in the range of 10-40 mg/day.

Transdermal delivery patches

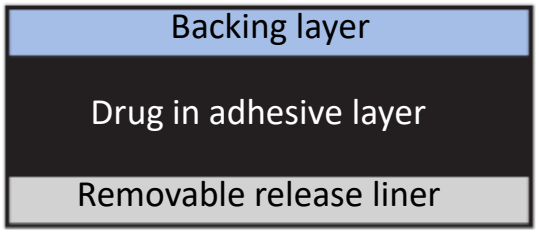
Are designed to deliver a constant and controlled dosage over extended periods of time for systemic therapy.

Due to the barrier properties of the skin, relatively few drug molecules have the appropriate physicochemical and therapeutic properties for sustained transdermal delivery. However some successful products have reached the market such as scopolamine, nicotine, estradiol, fentanyl, testosterone and glyceryl trinitrate transdermal patches.

Design of transdermal patches

Numerous patch design exist. The simplest systems contain the drug in an adhesive, with more complexity introduced in matrix type patches and reservoir systems.

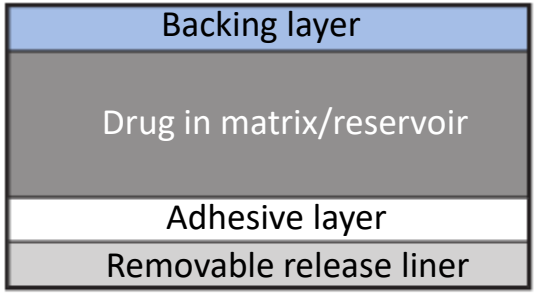
1. Drug-in-adhesive patches are the simplest and most common patch design and are widely used to deliver nicotine and glyceryl trinitrate.



Simple drug-in-adhesive patch

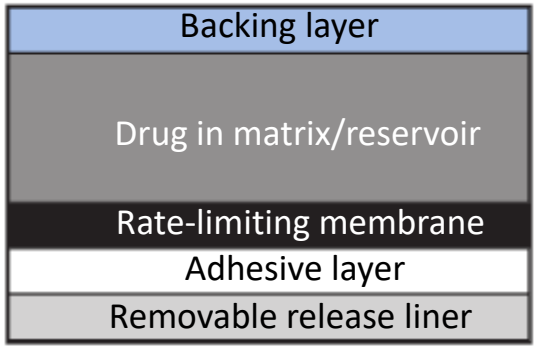
These patches are formed by dissolving or dispersing drug within an adhesive which is then coated onto a backing layer before a release liner is applied. Drug-in-adhesive patches tend to be thinner and more flexible than other systems, but drug loading constraints can reduce the period of delivery. For example, nicotine patches are designed for less than one day use.

2. Drugs can be included in a separate matrix which can be formulated to increase the drug content in the system, allowing longer term delivery. The drug containing matrix or reservoir is often a polymeric mixture, for example polyvinylpyrrolidone and polyvinylacetate, potentially with the addition of a plasticizer such as glycerol. Hydrogels may also be used as the matrix. Drug released from the matrix will partition into and diffuse through the adhesive layer.



Drug-in-matrix patch

3. More complex rate limiting membrane systems typically contain the drug in a reservoir but with release controlled through a semi-permeable membrane. The reservoir may be liquid or more often a gel and can be designed to contain higher drug loadings than a simple drug-in-adhesive system for prolonged delivery.



Rate-limiting membrane-type patch

For all the above configurations, patches have some common components:

- **Removable release liner:** A liner temporarily covers the adhesive and is the layer that is removed to allow the patch to be applied to the skin. Liners are often made from polymers such as ethylene vinyl acetate or aluminium foil dependent on the nature of the adhesive that it covers.

The liner must be easily peel away from the adhesive but must be bonded firmly enough to prevent accidental removal. Liners are usually occlusive to prevent the loss of volatile patch components such as ethanol prior to use.

- **Adhesive:** The adhesive is a crucial component of all transdermal delivery patches and pressure sensitive adhesives (PSAs) such as acrylates, polysiloxane adhesives are usually used. The adhesive must:

- Stick to the skin for the patch's lifetime.
- It must be non-irritating and non-allergenic as it may be in place for up to 7 days.
- It must be compatible with the drug and other excipients.
- It should allow the patch to be removed painlessly without leaving adhesive residue on the skin surface.

- **Backing layer:** Numerous materials can be used for patch backing layers, depending on the patch design, size and length of intended use. For relatively short use small patches, an occlusive backing layer may be selected and this will hydrate the underlying skin which can improve delivery. Example materials include polyethylene or polyester films. For larger and longer term use patches, backing layers that permit some vapour transmission are preferred such as polyvinylchloride films. In addition, the backing layer should allow multidirectional stretch and be pliable to allow the patch to move as the skin moves.

- **Matrix/reservoir:** A drug matrix or reservoir is usually prepared by dissolving the drug and polymers in a common solvent before adding in other excipients such as plasticizers.

The viscosity of the matrix can be modified by the amounts of polymers incorporated in the matrix and can consequently be used to control diffusion of the active ingredient through the matrix to the adhesive and then on to the skin surface.

- **Rate-limiting membrane:** semi-permeable membranes are used to separate reservoir from the underlying adhesive layer and designed to control the rate of delivery of the active ingredient to the skin surface. Membranes can be prepared from co-polymers of ethylene acetate with vinyl acetate with or without plasticizers. As with other patch components, the rate limiting membrane must be compatible with the drug, non-toxic, stable and pliable.

General clinical consideration in the use of TDDS

1. Percutaneous absorption may vary according to the site of application, there is a preferred application site stated in the literature of each product.

   The patient should be advised of the importance of using the recommended site and rotating locations within that site in the application of replacement patches. Rotating locations is important to allow the skin beneath a patch to regain its normal permeability characteristics after being occluded and also prevent the possibility of skin irritation. Skin sites may be re-used after a week.

2. TDDS should be applied to clean and dry skin areas that are relatively free of hair and not oily or irritated, inflamed broken area.

3. TDDS should not be physically altered by cutting (as in attempt to reduce the dose) since this would destroy the integrity of the system.

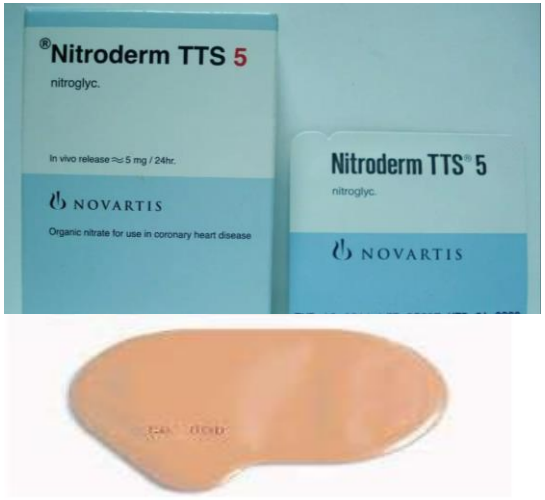
4. The protective removable release liner should be removed to expose the adhesive layer while being careful not to touch the adhesive surface which may contains drug to the finger tips. The patch should be pressed firmly against the skin site with the hand for 10 seconds to assure uniform contact and adhesion.

5. TDDS should be worn for the full period of time stated in the product's instructions and care should be taken not to touch the eyes or the mouth during handling of the system.

Examples of TDDS

1. **Transdermal Scopolamine:** used to prevent travel-related motion sickness, nausea and vomiting. The TDDS contains 1.5mg of scopolamine and is designed to deliver the drug at constant rate to the systemic circulation over 3 days. The patch is worn in a hairless area behind the ear.

2. **Transdermal Nitroglycerin:** designed to provide controlled release of nitroglycerin for the treatment of angina. Each patch delivers nitroglycerin over 24 hrs (Daily application) to the chest, shoulder and upper arm.



Nitroglycerin is rapidly metabolised by the liver when taken orally and therefore this effect can be prevented by the transdermal route. Nitroglycerin patch is available in two strengths 5mg and 10mg.

Transdermal Nicotine: are used in smoking cessation programmes. They have been shown to be an effective aid in quitting the smoking habit when used according to product-recommended strategies.

They provide sustained blood levels of nicotine as nicotine replacement therapy. The available patches contain from 7-22mg of nicotine for daily application for 6-12 weeks applied to the arm.