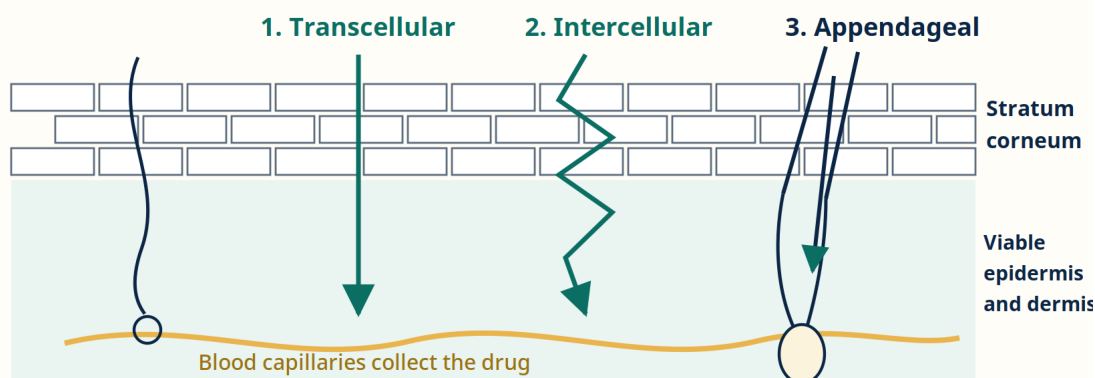


5.1 Structure of skin and the barrier

Skin is the largest organ of the body, about 2 square metres in an adult, and it is built to keep things out. Its layers, from the surface:

Routes of Penetration Across Skin



1 Through the corneocytes. 2 Between the cells, through the lipid mortar (the main route).

3 Shunt route via hair follicles and sweat ducts.

Surface of the skin is at the top; drug moves downwards towards the capillaries.

Figure: The three routes across the stratum corneum: transcellular, intercellular and appendageal.

- **Stratum corneum:** the outer 10 to 20 micrometres, the rate limiting barrier. Dead flattened cells (corneocytes) embedded in ordered lipid sheets of ceramides, cholesterol and free fatty acids; the standard description is a brick and mortar wall, bricks of keratin filled cells in a mortar of lipid. The drug mainly travels through the lipid mortar.
- **Viable epidermis:** living keratinocytes, about 50 to 100 micrometres, aqueous in character, contains enzymes that metabolise a small part of the dose.
- **Dermis:** connective tissue with the blood capillary network that collects the permeated drug into systemic circulation, plus the appendages, hair follicles and sweat glands, which offer a shunt route that matters mainly in the first minutes and for large or polar molecules.
- **Subcutaneous fat:** a depot and insulation layer below the dermis.

Permeation follows Fick's law in teaching form: flux rises with the partition coefficient into the stratum corneum, the diffusion coefficient within it and the concentration applied, and falls with barrier thickness. The ideal transdermal drug is therefore potent (daily dose in milligrams, ideally under about 10 to 20 mg per day), small (molecular weight under about 500), moderately lipophilic (log P about 1 to 4), low melting (which usually means better solubility in the barrier lipids) and non irritating.

5.2 Advantages and limitations of the transdermal route

Advantages: avoidance of first pass metabolism and of the gut environment, near constant input similar to an infusion without a needle, painless and self administered therapy, easy termination by removing the

patch, and improved compliance in chronic and motion sickness or pain therapy. **Limitations:** only a narrow set of drugs qualifies, onset is slow (a skin depot forms, so levels keep rising for hours and fall slowly after removal), skin irritation and sensitisation are the commonest practical failures, dose cannot be changed quickly, and cost per day is higher than oral therapy. Classic product examples to quote: nitroglycerin (angina prophylaxis), scopolamine (motion sickness, the first marketed patch system), fentanyl (severe chronic pain), nicotine (smoking cessation), estradiol and combined hormone patches, clonidine and rivastigmine.

5.3 Penetration enhancers

A penetration enhancer is a substance that reversibly reduces the barrier resistance of the stratum corneum. An ideal enhancer is non toxic, non irritating, reversible in action, compatible with drug and adhesive, odourless and cheap; no real enhancer meets every point, so selection is a compromise and concentration is a balance between flux gain and irritation.

Mechanisms and classes:

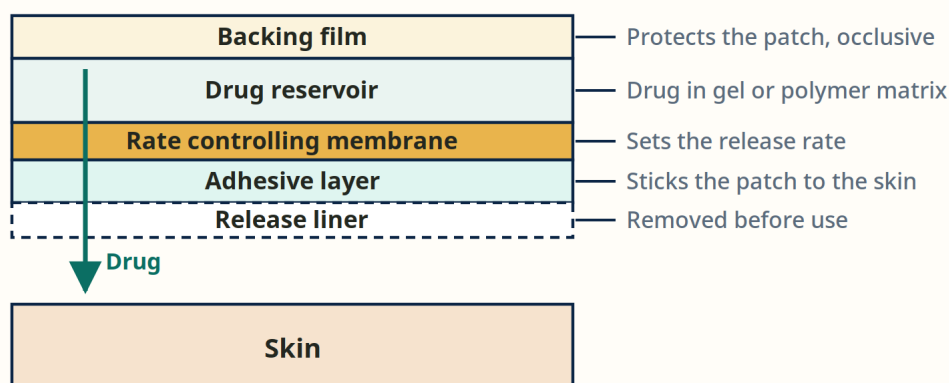
- **Lipid disruption:** oleic acid and other fatty acids, terpenes (menthol, limonene), and surfactants insert into the lipid sheets and disorder their packing, raising diffusion.
- **Solvent action:** ethanol, propylene glycol, Transcutol and dimethyl sulfoxide (DMSO) increase drug solubility in the barrier and partly extract lipids; ethanol is also the co solvent in several marketed gel and patch systems.
- **Keratolytic and keratin acting agents:** salicylic acid and urea soften and hydrate the corneocyte protein, opening the transcellular share of the route.
- **Hydration itself:** occlusion by the patch hydrates the stratum corneum, which swells corneocytes and can raise permeability several fold; every patch gets this effect free.
- **Physical enhancement** (device based, listed here because exams group them with enhancers): iontophoresis (current drives charged drug), electroporation (short high voltage pulses open temporary pores), sonophoresis (low frequency ultrasound), microneedles (microscopic projections that pierce only the stratum corneum, painless because they do not reach nerves), thermal ablation and microdermabrasion. Each one trades the chemical enhancer's simplicity for device cost and control.

Enhancer class	Examples	Main mechanism
Fatty acids	Oleic acid, lauric acid	Disorder stratum corneum lipids
Solvents and glycols	Ethanol, propylene glycol, DMSO	Raise drug solubility, extract some lipid
Terpenes	Menthol, limonene, cineole	Disrupt lipid packing, often low irritation
Surfactants	Sodium lauryl sulphate, Tweens	Interact with lipid and keratin, irritation risk
Keratolytics	Urea, salicylic acid	Hydrate and soften keratin

5.4 Transdermal systems: designs and components

A transdermal patch is an engineered stack. From outside in: an impermeable **backing layer** (protects and occludes), the **drug reservoir or drug in adhesive matrix**, a **rate controlling membrane** in reservoir designs, a pressure sensitive **adhesive layer** that also contacts skin in matrix designs, and a **release liner** removed before use. Overlay adhesive rings are added when edge lift is a risk.

Transdermal Patch: Layer Structure



Layers run from outside in: backing, reservoir, membrane, adhesive, liner.
The liner comes off first, then drug enters the skin at the membrane set rate.

Figure: Layers of a membrane controlled transdermal patch, outside in, with the release liner removed before use.

The four standard architectures:

Transdermal patch architectures

1. Reservoir system
Backing | Drug reservoir (gel/liquid) | Rate membrane | Adhesive | Liner
 2. Matrix system
Backing | Drug dispersed in polymer matrix | Adhesive | Liner
 3. Drug in adhesive system
Backing | Drug dissolved in the adhesive layer itself | Liner
 4. Microreservoir system
Backing | Drug in microscopic aqueous reservoirs within a lipophilic polymer matrix | Adhesive | Liner
- Rule: a reservoir patch must never be cut (dose dumping risk);
most matrix and drug in adhesive patches state their own rule on the label.

Reservoir systems give the most constant rate but carry dose dumping risk if the membrane is damaged. Matrix and drug in adhesive systems are thinner, simpler and safer on failure, with rate controlled jointly by the matrix and the skin itself.

5.5 Formulation and evaluation of transdermal systems

Formulation variables: drug loading and its physical state (dissolved versus suspended decides whether activity stays constant), polymer or adhesive choice (acrylic, silicone and polyisobutylene adhesives dominate), enhancer type and level, backing and liner compatibility, and the patch area, which is the dose dial: rate per square centimetre times area equals daily input, so strengths of one product are often just different patch sizes.

Evaluation set:

- **Physical and adhesive tests:** thickness and weight uniformity, drug content, moisture content and uptake, flatness, peel adhesion, tack and shear strength, and cold flow (adhesive creeping beyond the patch edge on storage).
- **In vitro permeation:** Franz diffusion cell studies across excised animal or human skin or a synthetic membrane, reporting flux, lag time and permeability coefficient; in vitro release testing through a membrane for quality control of the patch itself.

- **Stability and safety:** stability under ICH conditions with adhesion rechecked, skin irritation and sensitisation testing, and residual drug assay of used patches, because a fentanyl patch after use still holds a dangerous amount of drug and its disposal is a safety topic in itself.
- **In vivo confirmation:** pharmacokinetic studies showing the plateau profile, and adhesion performance scoring in volunteers under real wearing conditions (bathing, exercise, heat), since heat over a patch can raise absorption dangerously, a counselling point printed on most labels.