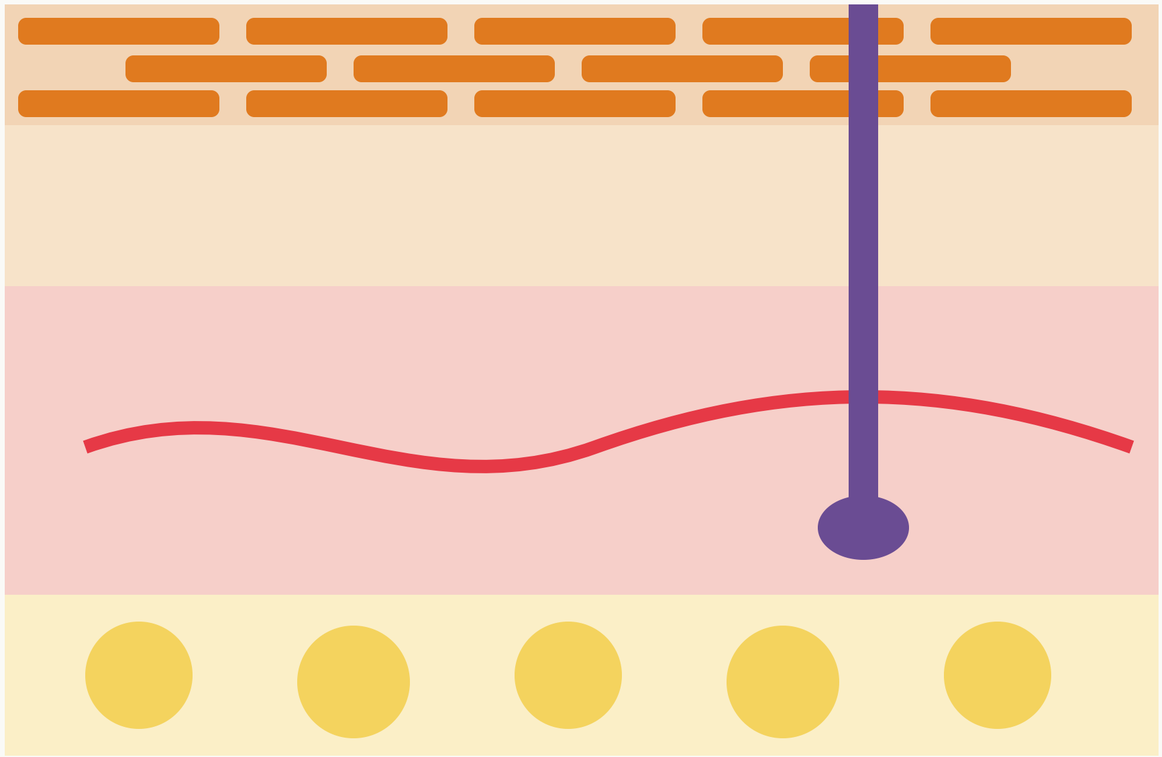
PRINCIPLES AND SYSTEMS OF DRUG DELIVERY · SEMINARS 15–17

Through the skin and under it: transdermal and implantable systems

Educational program “Pharmacy” · 4th year · Al-Farabi Kazakh National University

The skin barrier: “bricks and mortar”



Stratum corneum 10–20 µm: dead corneocytes in lipid matrix — main barrier

Viable epidermis: aqueous, enzymes

Dermis: capillaries take the drug into blood

Hair follicles: shunt route, ~0.1% of area

Seminar 15 · Elias PM, J Invest Dermatol 1983;80 Suppl:44s–49s; Prausnitz & Langer, Nat Biotechnol 2008;26:1261–1268

What makes a drug cross the skin?

< 500 Da

Small molecules diffuse faster

log P 1–3

Balanced: enter lipids, then leave into aqueous layers

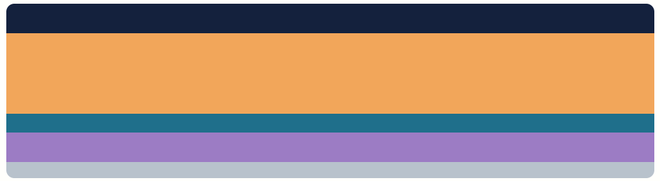
< 10 mg/day

Potent drug: low daily dose from a patch area

Flux through skin (Fick): **J = Kp · ΔC**, with Kp = D·K/h. Also: melting point < 200 °C, no skin irritation.

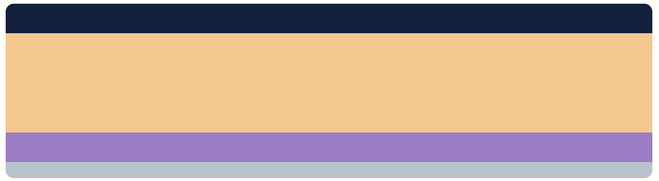
Types of transdermal therapeutic systems

Reservoir



Backing · drug reservoir · **rate membrane** · adhesive · liner. Zero order. Transderm-Scōp.

Matrix



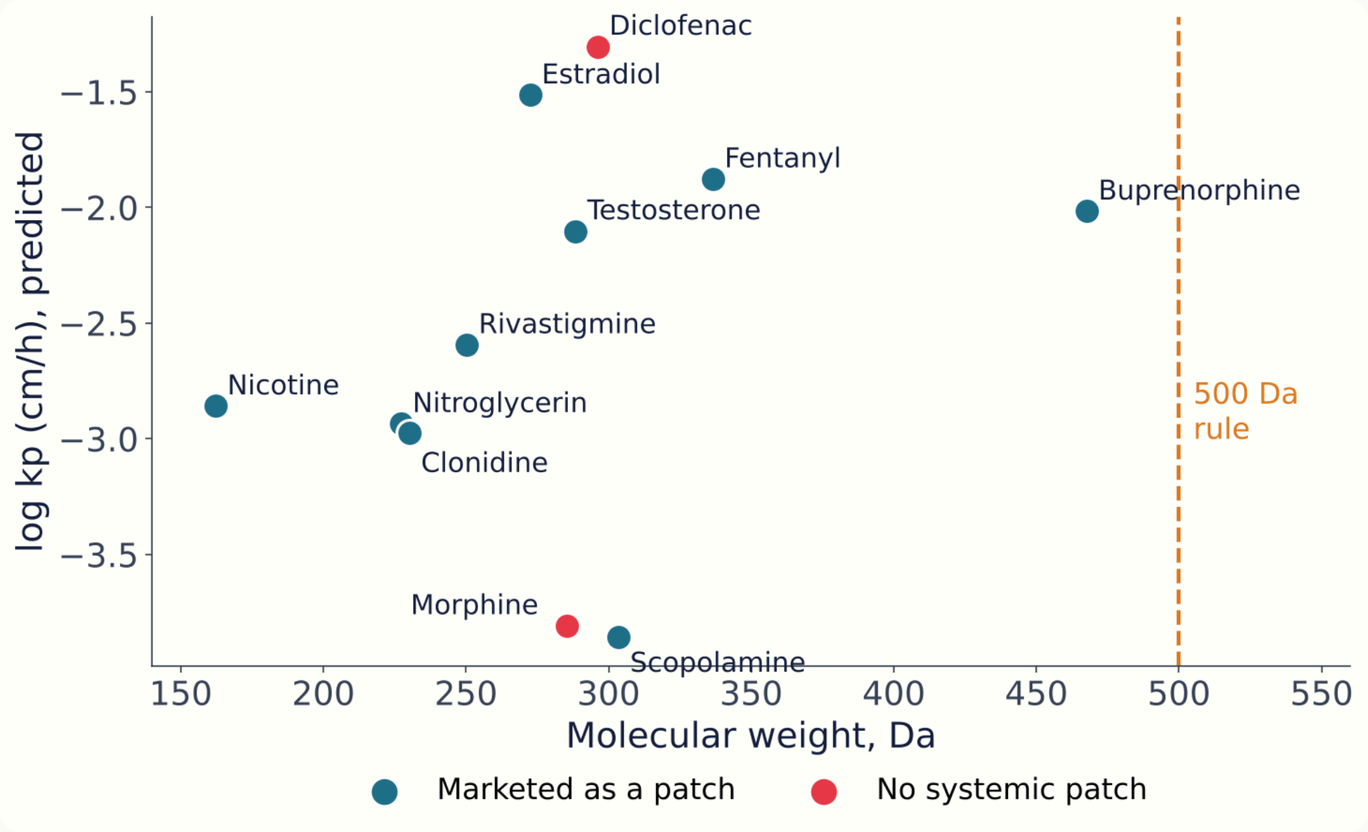
Drug dispersed in polymer matrix; skin controls rate. Older nitroglycerin patches.

Drug-in-adhesive



Drug in the adhesive itself; thin and discreet. Most modern patches (estradiol, fentanyl).

Predicting permeability: the Potts–Guy equation



log kp = −2.7 + 0.71·log P − 0.0061·MW

Permeability rises with lipophilicity and falls with size.

Diclofenac permeates well but needs 100+ mg/day — too much for a patch.

Marketed transdermal systems

Drug	Indication	Wear time	Note
Scopolamine	Motion sickness	3 days	First patch, 1979
Nitroglycerin	Angina	12–14 h on	Patch-free interval avoids tolerance
Nicotine	Smoking cessation	16–24 h	OTC
Estradiol	Menopause	3.5 or 7 days	No first-pass effect
Fentanyl	Chronic pain	72 h	Heat increases absorption
Rivastigmine	Alzheimer’s	24 h	Fewer GI side effects than capsules

Enhancing transdermal delivery

Chemical enhancers

Ethanol, oleic acid, propylene glycol, terpenes: disorder lipids, raise D and K

Iontophoresis

Small current drives ions: electrorepulsion and electroosmosis

Microneedles

Solid, coated, dissolving, hollow, hydrogel: bypass the stratum corneum

Sonophoresis, electroporation

Cavitation or short pulses create transient pores

Three generations: small lipophilic drugs → enhancers → physical disruption for proteins and vaccines.

Nanocarriers for dermal delivery

Carrier	Composition	Feature
Liposomes	Phospholipid + cholesterol	Depot in upper stratum corneum
Transfersomes	Phospholipid + edge activator	Ultra-deformable (Cevc, Germany)
Ethosomes	Phospholipid + 20–45% ethanol	Ethanol fluidises skin lipids
SLN, NLC	Solid (+ liquid) lipids	Occlusion, protect labile drugs (Müller, Berlin)
Nanoemulsions	Oil, water, surfactants	High solubilising power

Most act locally and through hair follicles, which collect particles of a few hundred nm.

Implantable systems: reservoir versus matrix

Reservoir



Drug core + rate-controlling membrane. **Zero order** while core is saturated. Risk: rupture → dumping.

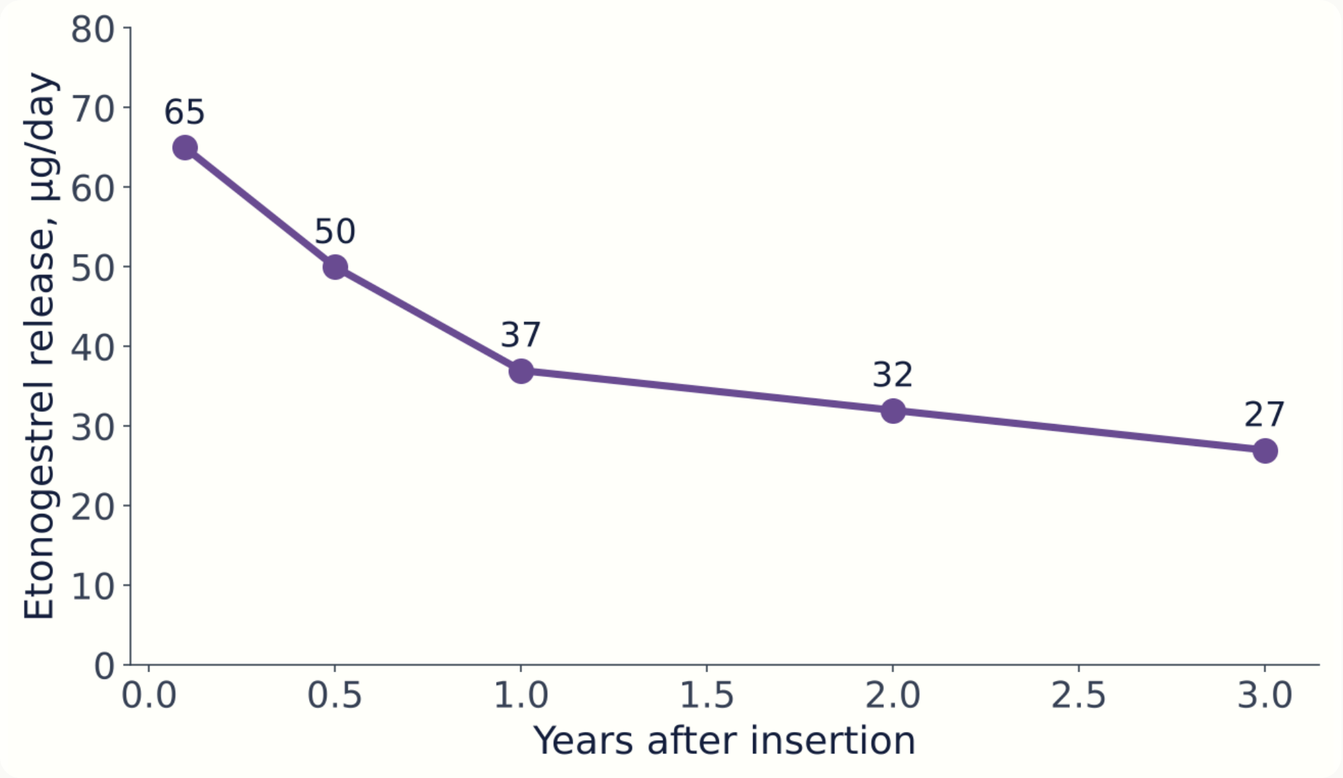
Matrix (monolithic)



Drug dispersed in polymer. Release falls with time (**√t**). Safe if damaged.

Non-degradable implants (silicone, EVA) must be removed; biodegradable ones (PLGA) disappear.

A matrix implant in practice: etonogestrel rod



4 cm × 2 mm EVA rod, 68 mg etonogestrel, subdermal in the upper arm

Release declines over time — typical **matrix** behaviour

Effective for 3 years; contains barium sulfate for X-ray location

Implants in clinical use

Product	Drug	Material, type	Duration
Nexplanon	Etonogestrel	EVA matrix rod	3 years
Jadelle	Levonorgestrel	Silicone, two rods	5 years
Zoladex	Goserelin	PLGA, biodegradable	1 or 3 months
Gliadel	Carmustine	Polyanhydride wafer in brain	2–3 weeks
Ozurdex	Dexamethasone	PLGA, intravitreal	Up to 6 months

Questions for discussion

1. Use Potts–Guy to explain why nicotine works as a patch and insulin does not.
2. Why must nitroglycerin patches be removed for 10–12 hours a day?
3. Which TTS type controls release by a membrane, and which by the skin?
4. Why is heat dangerous with a fentanyl patch?
5. Compare release curves of a reservoir and a matrix implant.
6. Why does Nexplanon contain barium sulfate?

References

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