BP805T · B.Pharm Semester VIII · Theory Notes

Sterile Dosage Forms and Novel Drug Delivery System

Unit III — Transdermal NDDS & Long-Acting Systems

Unit III (6 hours)

Pills & Python Notes

From-zero teaching standard: every technical term is defined before use.

Syllabus coverage: Unit III (6 hours).

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CHAPTER 4: Transdermal NDDS and Long-Acting Systems

Learning objectives

- Explain why transdermal (through-the-skin) delivery is needed, with advantages and disadvantages.
- Describe skin structure (stratum corneum, epidermis, dermis) and the three permeation pathways.
- Name the parts of a transdermal patch and each part's job.
- Explain permeation enhancers with examples and the irritation caution.
- Describe long-acting systems: in-situ gels, microspheres, implants, ocular inserts.
- Classify microneedles (solid, coated, dissolving, hollow) and explain iontophoresis and sonophoresis.
- Describe aseptic manufacturing basics, scale-up challenges and PAT.

Definitions

- **Transdermal drug delivery**: delivering a drug through unbroken skin into the blood, e.g. a patch on the arm.
- **Stratum corneum**: the outermost skin layer — dead, flattened cells packed with fats; the main barrier to drugs.
- **Epidermis**: the living skin layer below the stratum corneum, with no blood vessels.
- **Dermis**: the deeper skin layer with blood vessels, nerves, sweat glands and hair follicles.
- **Permeation**: movement of a drug across skin layers into the blood.
- **Permeation enhancer**: a chemical that temporarily loosens the skin barrier so more drug passes.
- **In-situ gel**: a liquid that turns into a gel inside the body, triggered by temperature, pH or ions.
- **Microsphere**: a tiny polymer ball carrying drug for slow release over weeks.
- **Implant**: a small device placed under the skin releasing drug over weeks or months.
- **Ocular insert**: a small device placed under the eyelid releasing drug slowly onto the eye.
- **Iontophoresis**: pushing a charged drug through skin using a very small electric current.
- **Sonophoresis**: using ultrasound waves to temporarily loosen the skin for drug passage.
- **Microneedle**: a patch of microscopic needles (<1 mm) piercing only the top skin layer, painlessly.
- **Aseptic manufacturing**: making a sterile product in a germ-free environment without final heat sterilisation.
- **Scale-up**: moving a formulation from laboratory batches to factory-size production.

- **PAT (process analytical technology)**: sensors checking quality *during* manufacturing, not only at the end.

Terminology

- **Flux**: drug crossing a unit skin area per unit time (e.g. mg/cm^2/h).
- **Rate-controlling membrane**: thin film controlling how fast drug leaves the patch — like a tap.
- **Backing layer**: outer waterproof cover stopping drug escaping outward.
- **Release liner**: protective sheet peeled off and discarded before applying the patch.
- **Pressure-sensitive adhesive**: sticky layer holding the patch on the skin.
- **Depot**: a stored drug reserve in the body (implant, microspheres) releasing drug slowly.
- **Lag time (skin)**: delay before drug first appears in blood after patch application.
- **Therapeutic window**: the blood-level range where the drug works without toxicity.

Explanation

4.1 Why transdermal delivery? Need, advantages, disadvantages

Many patients cannot swallow tablets well (children, elderly), some drugs irritate the stomach, and some are destroyed by the liver first (**first-pass metabolism**). A patch avoids these problems. **Advantages:** (1) no first-pass metabolism — drug enters blood directly through skin; (2) steady blood levels for hours/days, avoiding tablet peaks (side effects) and valleys (no effect); (3) easy to apply and stop — peel off if a side effect appears; (4) better compliance — one patch for days replaces many tablets; (5) no stomach irritation. **Disadvantages:** (1) skin is a strong barrier — only small, moderately fat-soluble drugs in low daily doses cross; (2) slow start — lag time of hours; (3) possible skin irritation/allergy from adhesive or enhancer; (4) unsuitable for emergencies or large doses. **Key takeaway:** patches suit small daily doses needing steady levels, not big or urgent doses.

4.2 Skin structure and permeation pathways

Three layers: (1) **Stratum corneum** — dead flat cells ("bricks") in fat layers ("mortar"); this wall gives almost all the resistance. (2) **Epidermis** — living cells, no blood vessels. (3) **Dermis** — blood vessels carry the drug into the body. Three pathways: **between the cells** (intercellular) — winding through the fatty mortar, the main route; **through the cells** (transcellular) — hard, alternating fat/water regions; **down hair follicles and sweat glands** (shunt) — under 1% of skin area. **Key takeaway:** the drug mostly squeezes through the fatty mortar between dead cells.

4.3 Transdermal patch structure and components

A patch is a sandwich: (1) **Backing layer** — outer waterproof film; stops drug escaping outward. (2) **Drug reservoir or matrix** — the storehouse; a *reservoir* patch holds drug as a liquid/gel pool, a *matrix* patch mixes drug evenly in a polymer layer. (3) **Rate-controlling membrane** (reservoir patches) — thin film acting like a tap, releasing drug at a fixed speed. (4) **Adhesive layer** — sticky layer holding the patch on skin. (5) **Release liner** — protective sheet peeled off and thrown away just before use. **Key takeaway:** each layer has one job — cover, store, control, stick, protect.

4.4 Permeation enhancers — types, examples, caution

Enhancers temporarily loosen the stratum corneum: **alcohols/glycols** (ethanol, propylene glycol) dissolve some skin fats; **fatty acids** (oleic acid) disturb the neat fat packing; **surfactants** (sodium lauryl sulphate) loosen fats and proteins; **terpenes** (menthol, eucalyptus oil) create temporary gaps in fat layers. **Caution:** enhancers work by slightly damaging the barrier — too much causes redness, itching, burning or allergy. Use the lowest effective level, and every new enhancer needs skin-irritation testing. "Natural" does not mean safe — plant oils can irritate too.

4.5 Long-acting systems

These form a **depot** releasing drug over days to months: **In-situ gels** — supplied as liquid (easy to inject/drop), then gel inside the body; triggers: **temperature** (liquid at room temperature, gels at 37 °C), **pH** (gels at body pH), **ions** (gels on meeting calcium/sodium in body fluids). Example: an eye drop liquid in the bottle that gels on the eye and stays longer. **Microspheres** — tiny polymer balls injected under skin/muscle; the polymer slowly erodes, releasing drug over weeks (one monthly injection instead of daily tablets). **Implants** — small rods/discs placed under the skin, releasing steadily for months; biodegradable ones dissolve away. **Ocular inserts** — placed under the eyelid; ordinary eye drops wash away in minutes, an insert stays hours/days — useful for glaucoma. **Key takeaway:** one small procedure buys weeks/months of freedom from daily dosing.

4.6 Advanced transdermal and microneedle technologies

Iontophoresis — a tiny battery current pushes charged drug molecules through skin (like charges repel, driving drug inward); painless, for drugs that cannot cross alone. **Sonophoresis** — ultrasound shakes the skin's fat layers, opening temporary pathways; reversible when it stops. **Microneedles** — hundreds of needles under 1 mm, crossing the stratum corneum but too short to reach nerves, so painless. Four types: **solid** ("poke and apply" — pierce, then apply drug cream); **coated** ("coat and poke" — drug coating dissolves off inside); **dissolving** ("poke and dissolve" — needles of drug + polymer melt in skin, nothing left behind); **hollow** ("poke and flow" — liquid injected through tiny hollow needles).

4.7 Aseptic manufacturing, scale-up challenges, PAT

Implants, microspheres, ocular inserts and microneedles **cannot be heat-sterilised** — heat would melt polymers or destroy drug. So they use **aseptic manufacturing**: ingredients sterilised separately (e.g. by filtration) and assembled in sterile clean rooms. **Scale-up challenges** (lab → factory): (1) uniformity — millions of identical microneedles/microspheres; (2) sterility at scale — a huge clean room is far harder to keep germ-free; (3) polymer behaviour changes between small and large vessels, altering release rate; (4) cost — sterile facilities and precision equipment are expensive. **PAT** places sensors *inside* the process (temperature, particle size, moisture, drug content) so drift is corrected immediately — like CCTV watching the cooking, not just tasting the finished dish. **Key takeaway:** sterile NDDS are built germ-free from the start, are hard to scale uniformly, and PAT watches quality live.

Classification

```
Transdermal NDDS & Long-Acting Systems
│
├── TRANSDERMAL PATCHES
│      ├── Reservoir patch (drug pool + rate-controlling membrane)
│      └── Matrix patch (drug mixed in polymer/adhesive layer)
│
├── PERMEATION ENHANCEMENT
│      ├── Chemical enhancers (alcohols, fatty acids, surfactants, terpenes)
│      ├── Iontophoresis (electric current pushes charged drug)
│      └── Sonophoresis (ultrasound loosens skin temporarily)
│
├── MICRONEEDLES
│      ├── Solid ("poke and apply") / Coated ("coat and poke")
│      └── Dissolving ("poke and dissolve") / Hollow ("poke and flow")
│
└── LONG-ACTING DEPOT SYSTEMS
       ├── In-situ gels (liquid → gel by temperature / pH / ions)
       ├── Microspheres (injectable, erode over weeks)
       ├── Implants (under-skin, months of release)
       └── Ocular inserts (under-eyelid, for the eye)
```

Mechanisms

Mechanism 1 — Skin permeation and Fick's law (simply)

Drugs cross skin by **diffusion**: high concentration (patch) → low concentration (blood). **Fick's law** in simple form: **delivery rate = permeability × patch area × drug concentration**. This tells us: double the area → double the drug; double the concentration → double the drug; if skin permeability is very low, even a big patch delivers little — which is why enhancers matter.

```
PATCH (high drug) → STRATUM CORNEUM (main barrier, slowest step)
→ EPIDERMIS → DERMIS (blood picks up drug → whole body)
```

Mechanism 2 — Microneedle penetration

```
Patch pressed on skin → needles (<1 mm) pierce ONLY stratum corneum
→ tiny channels open, nerves NOT reached (painless)
→ drug enters: solid → cream after; coated → coating dissolves;
  dissolving → needle melts; hollow → liquid injected
```

Mechanism 3 — Iontophoresis and sonophoresis

```
IONTOPHORESIS: battery (+) repels positively charged drug → pushed INTO skin
SONOPHORESIS: ultrasound vibrates skin fats → temporary gaps open
  → drug passes → ultrasound stops → gaps close (reversible)
```

Mechanism 4 — In-situ gelation triggers

```
LIQUID (syringe/dropper)
 ├─ temperature → gels at body temperature (37 °C)
 ├─ pH → gels at body pH
 └─ ions → gels on meeting Ca²⁺/Na⁺ in body fluids
 → GEL DEPOT → slow release over days/weeks
```

Mechanism 5 — Depot release (implants, microspheres)

- **Diffusion**: drug seeps through the polymer, like water through a clay pot. - **Erosion**: the polymer itself breaks down in body fluids, freeing drug — like a shrinking soap bar. Most depots use both: early release by diffusion, later release by erosion.

Diagrams and flowcharts

Diagram 1 — Skin layers and pathways

```
Skin surface
──────────────────────────────────
STRATUM CORNEUM  [■ ■ ■ ■]  ~mortar~   ← main barrier
──────────────────────────────────
EPIDERMIS        (living cells, no blood)
──────────────────────────────────
DERMIS           ≈≈ blood vessels ≈≈    ← drug enters blood
Pathways:  between cells (main)  through cells  hair follicles
```

Diagram 2 — Patch sandwich

```
┌──────────────────────────────────┐
│ BACKING (waterproof cover)       │
│ DRUG RESERVOIR / MATRIX          │ ← storehouse
│ RATE-CONTROLLING MEMBRANE        │ ← the "tap"
│ ADHESIVE (sticky)                │
│ RELEASE LINER (PEEL OFF & THROW) │
└──────────────────────────────────┘ → applied to skin
```

Diagram 3 — Microneedle types

```
SOLID → poke, then apply cream │ COATED → drug coated on needle
DISSOLVING → needle melts in skin │ HOLLOW → liquid flows through
```

Diagram 4 — PAT vs old QC

```
PAT: sensors at every step → correct drift immediately (CCTV in kitchen)
Old: test only finished batch → too late to fix (taste only the dish)
```

Infographic concepts

1 **"The brick wall"** — cartoon wall labelled stratum corneum; arrows: winding through mortar (main route), straight through bricks (hard), down a chimney/follicle (shunt).

2 **"Patch sandwich"** — burger-style stack of the five layers; peeling the bottom "liner" reveals the sticky side.

3 **"Four microneedles"** — four panels with 3-word captions (poke-and-apply, coat-and-poke, poke-and-dissolve, poke-and-flow) and a "painless ✓" badge.

Tables

Table 1 — Advantages vs disadvantages of transdermal delivery

Advantages	Disadvantages
Avoids first-pass liver metabolism	Only small, low-dose drugs cross skin
Steady blood levels for hours/days	Slow start (lag time of hours)
Easy to apply and stop (peel off)	Skin irritation/allergy possible
Better compliance (fewer doses)	Not for emergencies or large doses

Table 2 — Skin layers and pathways

Layer / Pathway	Key fact
Stratum corneum	Dead cells + fat "mortar" — main barrier
Epidermis	Living cells, no blood — drug passes through
Dermis	Blood vessels — drug enters blood here
Intercellular (between cells)	Main route for most drugs
Transcellular (through cells)	Minor — alternating fat/water is hard
Shunt (follicles, glands)	Small — under 1% of skin area

Table 3 — Patch components

Component	Job
Backing layer	Waterproof cover; stops outward drug loss
Drug reservoir/matrix	Storehouse of the drug
Rate-controlling membrane	"Tap" fixing release speed
Adhesive layer	Sticks patch to skin
Release liner	Peeled off and discarded before use

Table 4 — Microneedle types and long-acting systems

System	How it works
Solid microneedle	Poke and apply — cream enters the holes
Coated microneedle	Coat and poke — coating dissolves off
Dissolving microneedle	Poke and dissolve — needle melts away
Hollow microneedle	Poke and flow — liquid injected through
In-situ gel	Liquid → gel by temperature/pH/ions
Microspheres / implants	Depot releases by diffusion + erosion

Worked examples and calculations

Example 1 — Daily drug from a patch (Fick's law). Patch area 10 cm^2, flux 0.05 $mg/cm^2/h$. Drug delivered in 24 h?

- Step 1: per hour = 0.05 × 10 = **0.5 mg/h**.
- Step 2: in 24 h = 0.5 × 24 = **12 mg/day** — only potent low-dose drugs qualify.

Example 2 — Doubling the patch area. Same patch at 20 cm^2?

- Step 1: per hour = 0.05 × 20 = **1.0 mg/h**; in 24 h = **24 mg/day**.
- Meaning: delivery is proportional to area — double area, double dose.

Example 3 — Microsphere depot daily release. 300 mg drug in microspheres releasing steadily over 30 days.

- Step 1: daily release = 300 ÷ 30 = **10 mg/day** — one injection replaces 30 daily tablets.

Example 4 — Patch lag time. Pain patch: 4 h lag, then works 72 h. Applied 6:00 AM Monday.

- Step 1: relief begins 6:00 AM + 4 h = **10:00 AM Monday**.
- Step 2: change patch at 6:00 AM Monday + 72 h = **6:00 AM Thursday**.
- Meaning: another painkiller is needed for the first 4 h — patches are not instant.

Analogies

1. **Stratum corneum = brick wall with mortar** — drug squeezes through the mortar gaps (intercellular route).
2. **Rate-controlling membrane = water tap** — reservoir is the tank; the membrane lets drug out drop by drop.
3. **Permeation enhancer = loosening a jar lid** — temporary loosening, not breaking; too much force cracks the jar (irritates skin).
4. **Implant = slow soap bar** — shrinks a little each day, releasing steadily.
5. **Iontophoresis = repelling magnets** — like charges push the charged drug into the skin.
6. **PAT = CCTV in the kitchen** — watches every step live; old QC only tastes the finished dish.

Pharmacy relevance

- **Chronic diseases:** patches/implants give steady levels for long treatments, improving compliance.
- **Cannot swallow:** children, elderly and unconscious patients benefit from patches, gels, microneedles.
- **Vaccination future:** dissolving microneedle patches could allow painless vaccination without trained injectors.
- **Pharmacist's role:** counsel on correct application (clean dry skin, rotate sites, never cut a reservoir patch) and warn that patches are not instant relief.
- **Careers:** aseptic manufacturing and PAT are high-skill areas needing trained pharmacists.

India context

- **Rural relevance:** a monthly injection or multi-day patch suits patients travelling far to health centres.
- **Eye care need:** with India's large glaucoma population, inserts reducing drop frequency matter greatly.

- **Make-in-India:** aseptic NDDS plants need trained graduates; scale-up and PAT skills are in demand in pharma hubs (Hyderabad, Ahmedabad, Mumbai, Bengaluru).
- **Climate caution:** in hot, humid weather, sweating under patches raises irritation risk — site rotation and skin checks matter more.
- **Regulatory note:** sterile/novel products are evaluated as per the latest CDSCO/DCGI guidelines — confirm the current edition.

Key points

- Fick's law simply: delivery = permeability × area × concentration.
- Long-acting depots (in-situ gels, microspheres, implants, ocular inserts) release over days–months by diffusion + erosion.
- Microneedles: solid, coated, dissolving, hollow — painless (do not reach nerves).
- Iontophoresis = electric current; sonophoresis = ultrasound.
- Sterile NDDS need aseptic manufacturing; scale-up challenges are uniformity, sterility, cost; PAT monitors quality live.

Common confusions

1. **Transdermal vs topical** — transdermal reaches the blood (whole-body effect); topical acts only on the skin.
2. **Reservoir vs matrix patch** — reservoir has a drug pool + membrane; matrix mixes drug in the polymer/adhesive.
3. **Release liner vs backing** — liner is peeled off and discarded; backing stays as the outer cover.
4. **Iontophoresis vs sonophoresis** — electric current vs ultrasound; different energy, different mechanism.
5. **Aseptic manufacturing vs terminal sterilisation** — aseptic builds germ-free from the start; terminal sterilises the finished sealed product. Heat-sensitive NDDS cannot use terminal heat.

Common mistakes

1. Cutting a reservoir patch for a smaller dose — destroys the membrane and dumps the whole drug pool (dose dumping).
2. Expecting instant relief — forgetting the skin lag time of hours.
3. Applying on oily, hairy or broken skin — poor sticking, unpredictable absorption.
4. Using too much enhancer — redness, itching, allergy; more enhancer ≠ safely more drug.
5. Claiming any drug can become a patch — only potent, small, fat-soluble, low-dose drugs qualify.
6. Testing quality only at the end and calling it PAT — PAT monitors *during* the process.

Mnemonics

1 **Patch layers — "B-D-R-A-L": B**acking, **D**rug reservoir/matrix, **R**ate membrane, **A**dhesive, **L**iner (peel off).

2 **Skin layers — "SED": S**tratum corneum, **E**pidermis, **D**ermis (top to bottom).

3 **Microneedles — "SCDH": S**olid (poke-apply), **C**oated (coat-poke), **D**issolving (poke-dissolve), **H**ollow (poke-flow).

4 **In-situ gel triggers — "TIP": T**emperature, **I**ons, **P**H.

Exam summary

Transdermal delivery sends drugs through unbroken skin into blood, avoiding first-pass metabolism with steady levels for days — but only small, low-dose drugs qualify, lag time is hours, and irritation is a risk. The stratum corneum (dead cells + fat "mortar") is the main barrier; drugs mainly cross between cells. A patch has backing, drug reservoir/matrix, rate-controlling membrane, adhesive and peel-off release liner. Enhancers temporarily loosen the barrier but must stay low to avoid irritation. Fick's law: delivery = permeability × area × concentration. Long-acting depots — in-situ gels, microspheres, implants, ocular inserts — release over days–months by diffusion and erosion. Microneedles (solid, coated, dissolving, hollow) painlessly bypass the barrier; iontophoresis uses current, sonophoresis ultrasound. Heat-sensitive sterile NDDS use aseptic manufacturing; scale-up challenges are uniformity, sterility, cost; PAT monitors quality live.

One-minute revision

Barrier = stratum corneum (brick + mortar). Patch: **B-D-R-A-L**. Fick: delivery = permeability × area × concentration. Microneedles **SCDH**, all painless. Gel triggers: **TIP**. Depot = diffusion + erosion. Sterile NDDS = aseptic making. PAT = live quality watch.

MCQs

1 The main barrier to transdermal delivery is the: (a) Dermis (b) Stratum corneum (c) Epidermis (d) Hypodermis — **Answer: (b)**

2 The main permeation pathway for most drugs is: (a) Hair follicles only (b) Between the cells, through fat layers (c) Directly through blood vessels (d) Sweat evaporation — **Answer: (b)**

3 Which patch layer is peeled off before application? (a) Backing (b) Rate-controlling membrane (c) Release liner (d) Drug reservoir — **Answer: (c)**

4 The rate-controlling membrane's job is to: (a) Stick the patch on (b) Control the speed of drug release (c) Block sunlight (d) Absorb sweat — **Answer: (b)**

5 A major advantage of transdermal over oral delivery is: (a) Faster emergency action (b) Avoidance of first-pass liver metabolism (c) Very large doses possible (d) No lag time — **Answer: (b)**

6 Which is a permeation enhancer? (a) Oleic acid (b) Lactose (c) Talc (d) Starch — **Answer: (a)**

7 The main caution with permeation enhancers is: (a) High cost (b) Possible skin irritation/allergy (c) They stop release (d) They dissolve the patch — **Answer: (b)**

8 An in-situ gel is administered as a: (a) Ready gel (b) Liquid that gels inside the body (c) Dry powder (d) Gas — **Answer: (b)**

9 Microspheres release drug mainly by: (a) Instant dissolving (b) Diffusion and polymer erosion (c) Magnetic force (d) Evaporation — **Answer: (b)**

10 An ocular insert is placed: (a) In the stomach (b) Under the eyelid / on the eye surface (c) In the nose (d) On the tongue — **Answer: (b)**

11 Iontophoresis pushes drug through skin using: (a) Small electric current (b) Ultrasound (c) Heat (d) Hand pressure — **Answer: (a)**

12 Sonophoresis uses which energy? (a) Electric current (b) Ultrasound waves (c) Laser (d) Magnetism — **Answer: (b)**

13 Which microneedle type melts away in the skin? (a) Solid (b) Coated (c) Dissolving (d) Hollow — **Answer: (c)**

14 Microneedles are painless mainly because they: (a) Contain anaesthetic (b) Are too short to reach nerves (c) Are soft rubber (d) Vibrate fast — **Answer: (b)**

15 Aseptic manufacturing is needed for sterile NDDS because: (a) It is cheaper (b) Heat would damage the polymer or drug (c) It needs no clean room (d) It is the fastest method — **Answer: (b)**

16 PAT means: (a) Testing only the finished product (b) Monitoring quality live during manufacturing (c) Testing packaging only (d) Animal testing — **Answer: (b)**

Viva and application questions

1 Why is transdermal preferred for drugs destroyed by the liver? — **Drug enters blood through skin, bypassing first-pass metabolism.**

2 Describe the stratum corneum in one line. — **Outermost dead-cell-plus-fat layer — the main barrier to drug entry.**

3 Name the five parts of a patch. — **Backing, drug reservoir/matrix, rate-controlling membrane, adhesive, release liner.**

4 Why must a reservoir patch never be cut? — **Cutting destroys the membrane and dumps the whole drug pool at once.**

5 State Fick's law simply. — **Delivery rate = skin permeability × patch area × drug concentration.**

6 Name a permeation enhancer and its caution. — **Oleic acid; excess causes skin irritation, so use the lowest effective level.**

7 How does an in-situ gel work? — **Applied as liquid; gels inside the body on temperature, pH or ion trigger, forming a slow-release depot.**

8 Name the four microneedle types. — **Solid, coated, dissolving, hollow.**

9 Iontophoresis vs sonophoresis? — **Electric current pushing charged drugs vs ultrasound temporarily loosening skin.**

10 What is PAT and its advantage? — **Live in-process quality monitoring with sensors; problems are fixed immediately, not found too late.**

References

- Vyas, S. P. and Khar, R. K. *Targeted and Controlled Drug Delivery: Novel Carrier Systems* — confirm the current edition.
- Ansel's *Pharmaceutical Dosage Forms and Drug Delivery Systems* — confirm the current edition.
- Aulton's *Pharmaceutics: The Design and Manufacture of Medicines* — confirm the current edition.
- PCI model syllabus and latest CDSCO/DCGI guidance for transdermal and sterile NDDS — as per the latest guidelines, confirm the current edition.