Transdermal drug delivery systems

INTRODUCTION

- TDDS are topically administered medicaments in the form of patches that deliver drugs for systemic effects at predetermined and controlled rate.
- Transdermal patch is an adhesive patch, that has a coating of medicine (drug), that is placed on the skin to deliver specific dose of the medicine, into the blood over a period of time.

History

1. The **first Transdermal patch was approved in 1981 to** prevent the nausea and vomiting associated with motion sickness.
2. The FDA has approved, till 2003, more than transdermal patch products, spanning **13 molecules.**
3. The US Transdermal market approached $1.2 billion in 2001. It was based on 11 drug molecules: fentanyl, nitroglycerin, estradiol, ethinyl estradiol, norethindrone acetate, testosterone, clonidine, nicotine, lidocaine, prilocaine, and scopolamine.
4. **Two new, recently approved Transdermal patch** products (a contraceptive patch containing ethinyl estradiol and nor-elgestromin, and a patch to treat overactive bladder containing oxybutynin.)

Advantages:

1. Avoids first pass hepatic metabolism.
2. Maintains constant blood levels for longer period of time.
3. Decrease the dose of administration.
4. Decrease unwanted/ side effects.
5. Decreases gastro-intestinal side effects.
6. Easy to discontinue in case of toxic effects.
7. Increased patient compliance.
8. Great advantage for patients who are unconscious.
9. Provides an ability to modify the properties of biological barriers to improve absorption.
10. Relatively large area of application in comparison to buccal / nasal cavity.

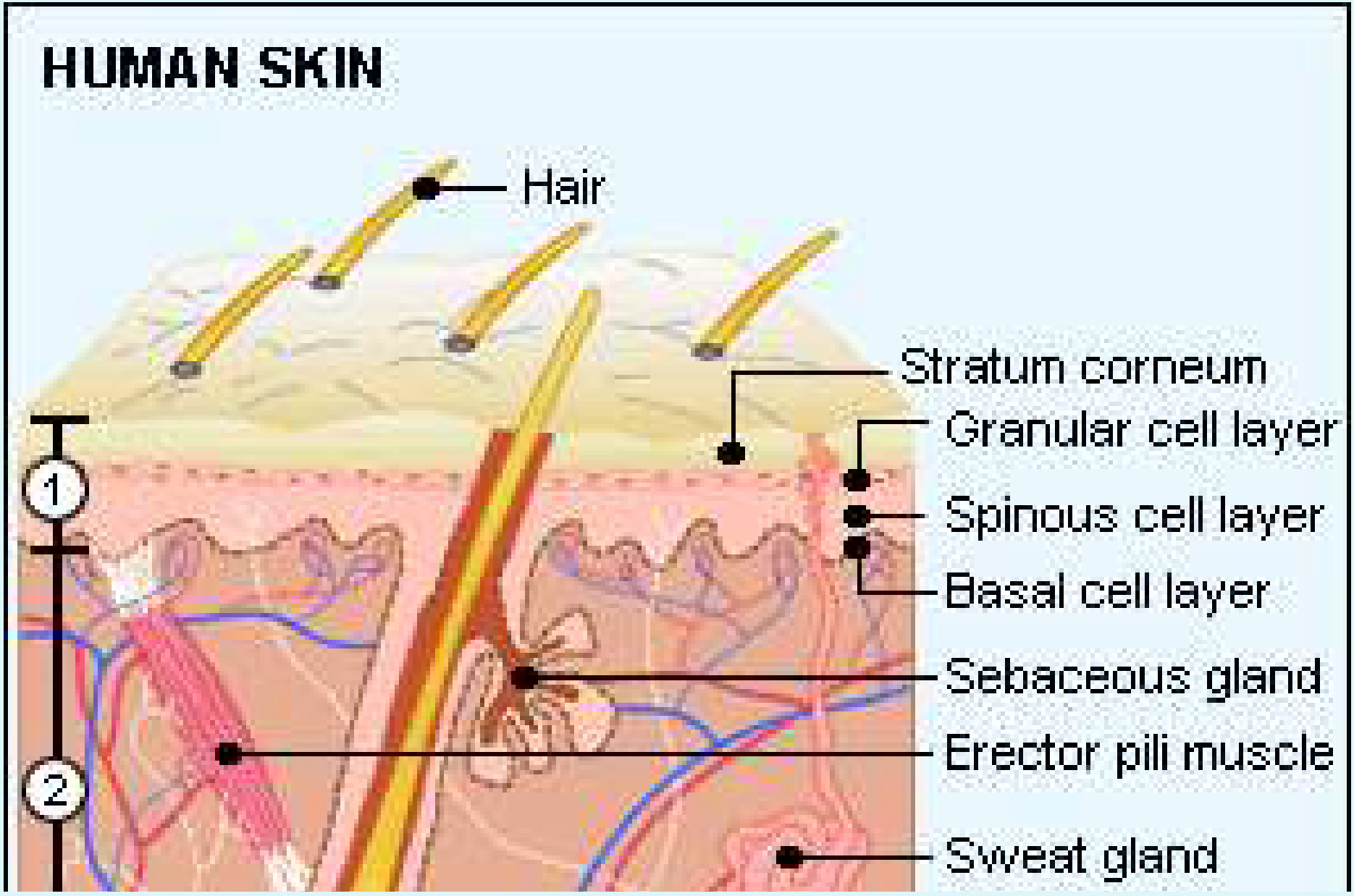
disadvantages

1. Drug must have some desirable physico-chemical properties to penetrate through stratum conium.
2. Drugs for daily dose less than 5 mg/day are preferred, If drug dose is more than 10-25 mg/day the TDD will be difficult.
3. Local irritation at the site of administration may be caused by drug, adhesive/ other excipients in patch.
4. Clinical need must be clearly established.
5. The barrier function of skin changes form one site to another, from person to person and with age.
6. Poor skin permeability limits the number of drug that can be delivered in this route.
7. TDD can not deliver ionic drug.
8. TDD can not achieve high drug levels in Blood/ plasma.
9. Drugs of large molecular size can not be formulated as

COMPARISON BETWEEN IV,ORAL AND TDDS

ADVANTAGES	IV	ORAL
Avoid hepatic first-pass effects	YES	NO
Constant drug levels	YES	NO
Self-administration	NO	YES
Termination of therapy	NO	YES

ANATOMY AND PHYSIOLOGY OF SKIN



- Skin is the part of **Integrated system i.e. it helps to** maintain body temp and protect It from surrounding environment.
- It covers an area of about **2m2 and 4.5-5 kg i.e. about 16% of total body weight in adults.**
- Thickness is in range of **0.5mm (on eyelids) to 4.0mm(on heels).**

SKIN STRUCTURE

1. Non-viable epidermis (stratum corneum):

- Outer most layer of skin and physical barrier to most of the substances. It is 10-20 cell layer thick with lipids (5-15%), proteins (75-85%) mainly keratin.

2. Viable epidermis:

- This layer is in between stratum corneum and dermis (Stratum Granulosam, Spinosum & Basale) with 50-100 µm thickness & 90% water content.

3. Viable dermis (cornium):

- Thickness is 2000-3000 µm, consists of matrix of loose connective tissue composed of fibrous protein (collagen, elastin, reticulum)

4. Subcutaneous connective tissue (hypodermis):

- It has loose textured white, fibrous connective tissue with fat and elastic fibers. It contains blood, lymph vessels, base of hair follicles, secretory portion of sweat glands and cutaneous nerves.

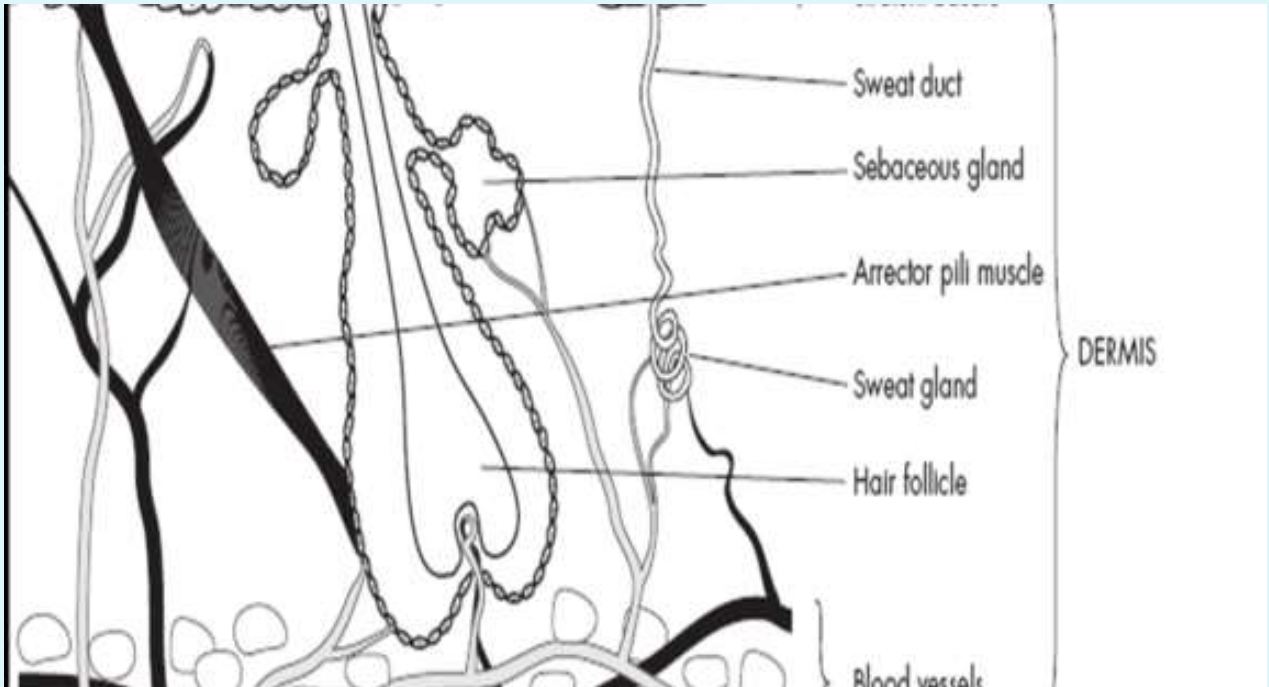
- Skin has mainly 3 layers...
  1)Epidermis
- Stratum Cornium
- Stratum Granulosm
- Stratum Spinosum
- Stratum Basal
  2)Dermis
  3)Subcutaneous layer

EPIDERMIS

- **Stratum Cornium- consists of 25 to 30 layers of** flattened dead keratinocytes. Which makes it water repellent.
- **Stratum Granulosm- consists of 3 to 5 layers and** under goes Apoptosis. It contains granules known as Keratohyalin. These granules release Lipid rich secretion, which acts as the water repellent.
- **Stratum Spinosum- contains 8 to 10 layers of cells** and it is closely arranged.
- **Stratum Basal- consists of single layer of cubical or** columnar keratinocytes.

DERMIS

- Composed of **strong connective tissue containing** collagen and elastic fibres, hence it can easily stretch and recoil easily.
- **Blood vessel, nerves gland and hair follicles are** embedded in this layer.

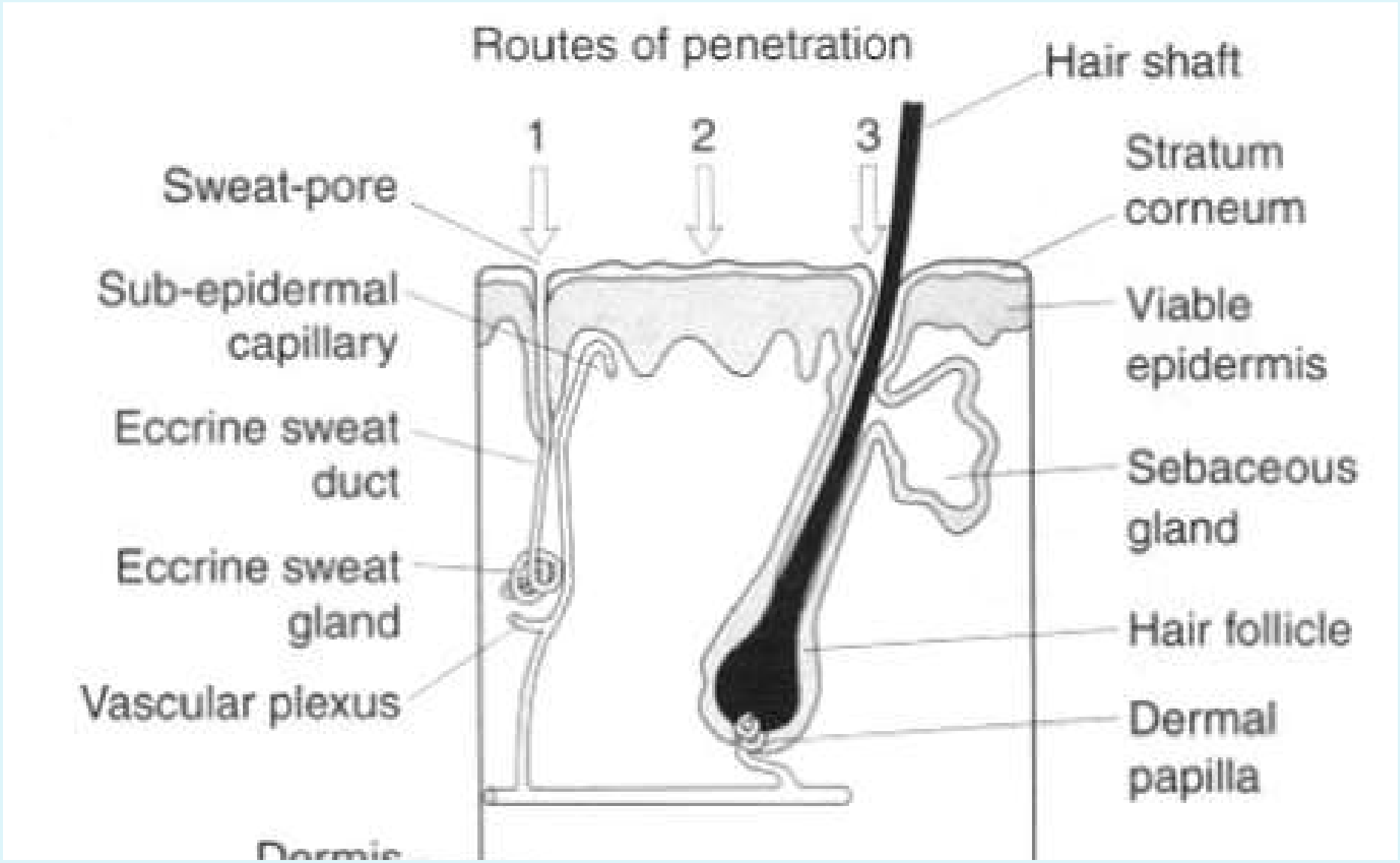


SUBCUTANEOUS LAYER

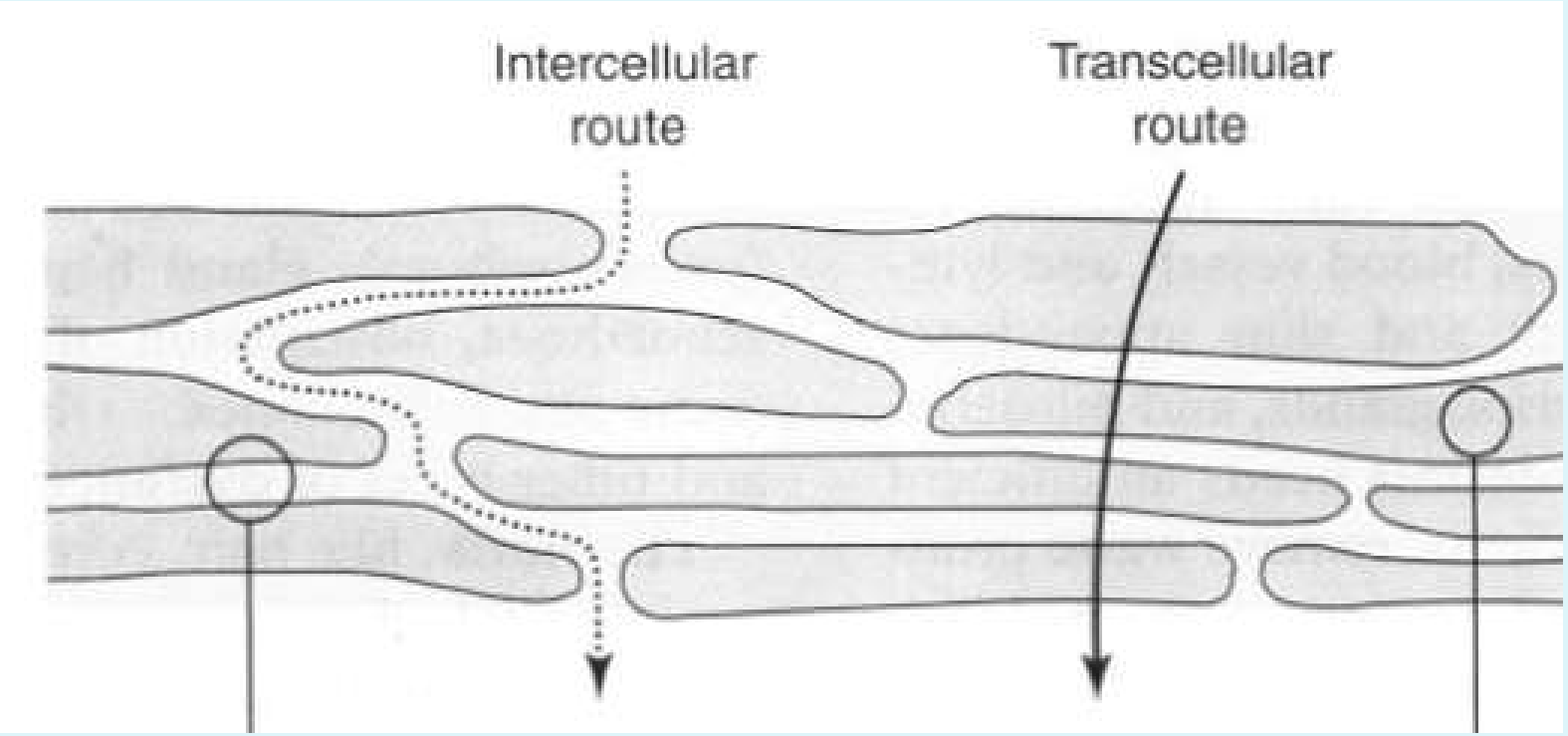
- It is also called as **Hypodermis.**
- It is made up of loose connective tissue, including **Adipose tissue.**
- This helps to insulate the body by monitoring heat gain and heat loss.
- The dermis is the layer of tissue that is Deeper and Thicker than epidermis

Routes of drug penetration across skin

- Three potential entry MACRO ROUTES to the viable tissue:
  1. Via the sweat ducts
  2. Across the continuous stratum corneum (diffusion)
  3. Through the hair follicles with their associated sebaceous glands.


Routes of penetration
Hair shaft
1
2
3
Sweat-pore
Stratum corneum
Sub-epidermal capillary
Viable epidermis
Eccrine sweat duct
Sebaceous gland
Eccrine sweat gland
Hair follicle
Vascular plexus
Dermal papilla

1. Transcellular permeation through the stratum corneum.
2. Intercellular permeation through the stratum corneum.
3. Transappendageal permeation via hair follicle, sebaceous & sweat gland.

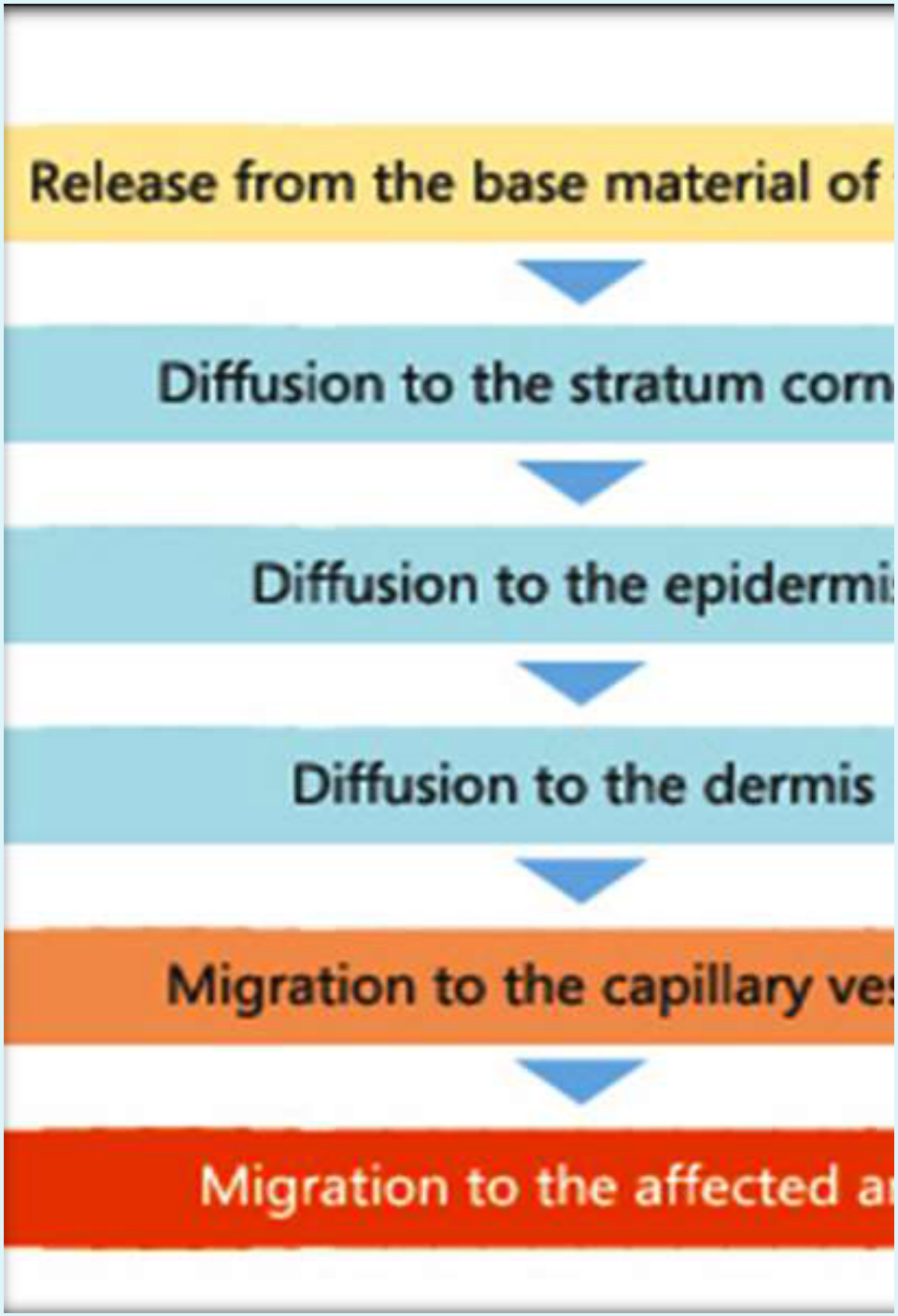


- Transcellular and inter cellular permeation requires diffusion through epidermis and dermis.
- Transappendageal permeation allows diffusional leakage of polar molecules in to epidermis and direct permeation in to dermis.
- The relative importance of these routes depends on factors like time of permeation, physico-chemical properties (Pka, molecular size, stability, partition coefficient), integrity and thickness of stratum corneum, density of sweat glands and follicles, skin hydration, metabolism and vehicle effects.

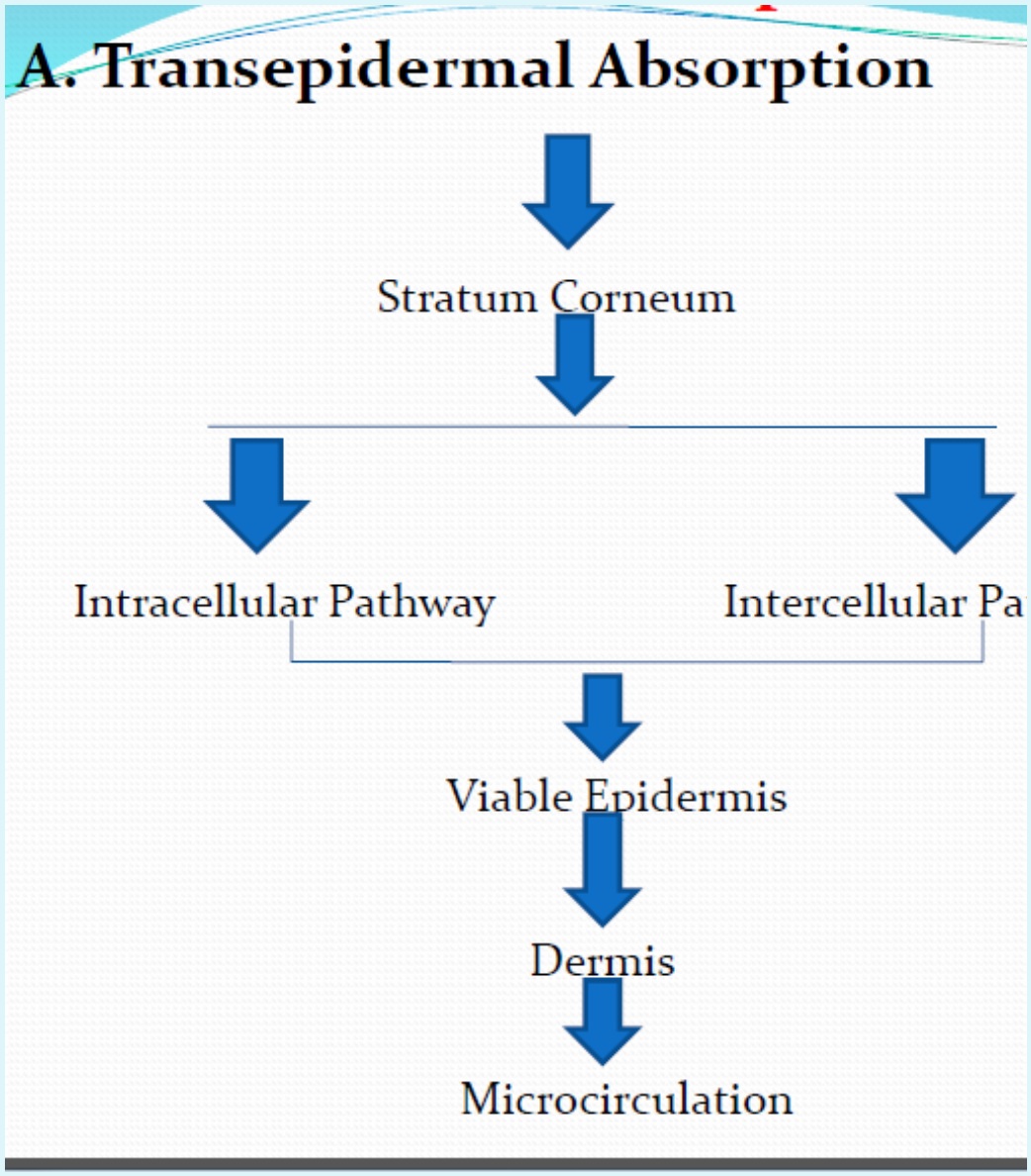
Mechanism of precutaneous drug absorption

- Transepidrmal pathway is responsible for drug diffusion across the skin.
- Permeation by the transepidermal route first involves partitioning in to stratum corneum.
- Most substances diffuse cross stratum corneum via intercellular lipiodal route which is tortuous pathway.
- Extremely polar compounds and ions pass by microscopic path through stratum corneum.
- Lipophilic molecules concentrate in and diffuse easily through the horny layers.
- When permeating drug exists stratum corneum, it enters wet cell mass of viable epidermis.

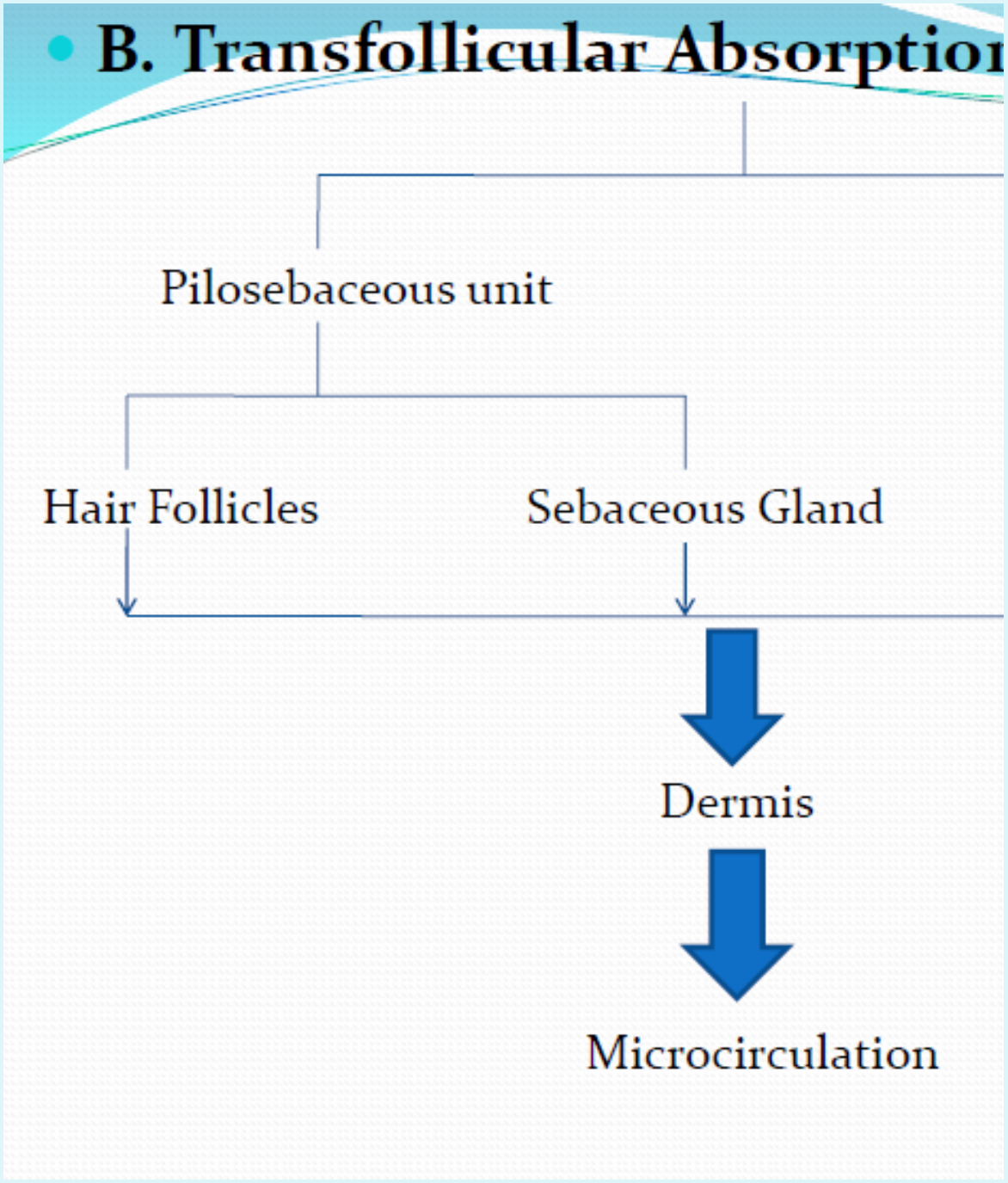
- As epidermis has no direct blood supply, the drug is forced to diffuse across it to reach the vasculature.
- The viable epidermis is a permeable field that functions as a viscid watery regimen to most penetrants.
- Extremely hydrophilic (Ions and polar non-electrolytes), extremely hydrophobic (lipophilic non-electrolytes) have difficulty in passing through viable epidermis.
- The epidermal cell membranes are tightly joined and there is little inercellular space for ions and polar nonelectrolytes to diffusionally squeeze through.
- Permeation in viable epidermis requires frequent crossing of cell membrames, which is prohibitive


Release from the base material of
Diffusion to the stratum corn
Diffusion to the epidermi
Diffusion to the dermis
Migration to the capillary ve
Migration to the affected a

Percutaneous absorption done by 2-ways

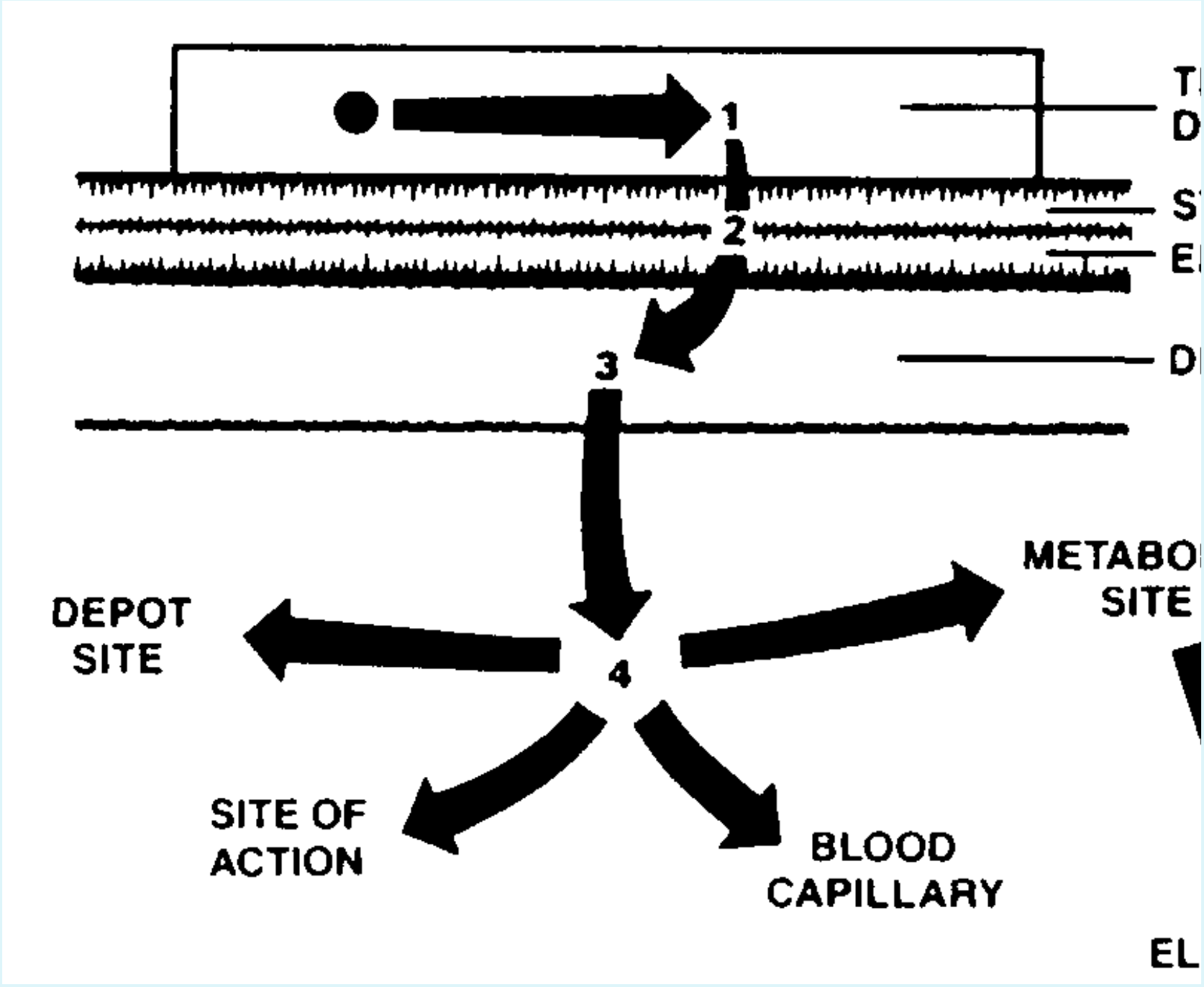


B. Transfollicular Absorption



Trans appendageal route

- Fractional area available through this route is 0.1 %
- Human skin contains 40-70 hair follicles, 200 to 250 sweat glands on every sq.cm of skin area.
- Mainly water soluble substance are diffused faster through appendages than that of other layers.
- Sweat glands and hair follicles act as a shunt i.e. easy pathway for diffusion through rate limiting ST corneum.
- Follicular route is important for permeation because the opening of the follicular pore is relatively large and sebum aids in the diffusion of the penetrant.
- Partitioning into the sebum followed by the diffusion to the depths of the epidermis is the mechanism of drug permeation.


1
2
3
4
DEPOT SITE
SITE OF ACTION
BLOOD CAPILLARY

- The Permeability coefficient at steady state (Pss) of the skin tissue to the drug is given by

$$Pss = Ks \times Dss / Hs$$

- Where

  Ks = partition coefficient of drug in to stratum corneum.

  Dss = apparent diffusivity for the steady state diffusion of the drug.

  Hs = over all thickness of skin tissue.

- The Flux (Jss) of the penetrating drug is given by

$$Jss = Pss \times Cveh.$$

- Where

  Jss = steady stste flux

  Cveh = concentration of drug in vehicle/ formulation.

Factors influencing dermal penetration of drugs

I. Biological factors:

1. Skin condition
2. Skin age
3. Blood flow
4. Regional skin site
5. Skin metabolism
6. Species difference.

II. Physicochemical factors:

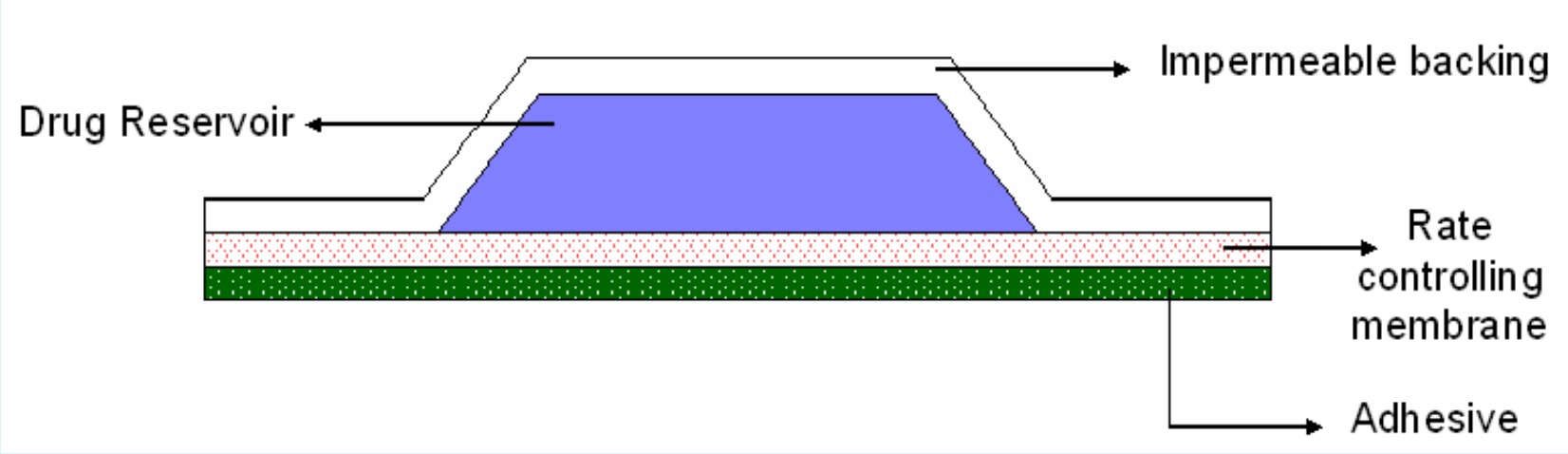
1. Skin hydration
2. Temperature and pH
3. Diffusion coefficient
4. Drug concentration
5. Partition coefficient
6. Molecular size and shape.
7. Solubility, ionization, M.pt

- Increase in Conc. of drug in vehicle increases amount of drug absorbed per unit of surface area per time interval.
- The drug in vehicle must interface the skin surface in sufficient conc.
- More drug is absorbed when it is applied to large surface area.
- Drug should have greater physicochemical attraction to the skin than to dispersed vehicle.
- The aqueous solubility of drug determines the conc. present at the absorption site.
- The partition coefficient influences the rate of transport across the absorption site.

- Solutes with molecular weight 800-1000 daltons, with adequate solubility in mineral oil and water (> 1mg/ml) can penetrate through skin.
- Drug absorption enhances form vehicles that easily covers the skin surface, mix readily with sebum.
- Vehicle that increases the amount of moisture imbedded by the skin improves drug absorption
  ex: oleagenous vehicles.
- Hydration of the skin softens stratum cornium, increases the size of pores, allowing greater flow of substances.
- Site of application influences degree of drug absortion. Skin in post auricular layer is more permeable to drugs.

Materials employed/ Formulation/ Components of transdermal patch

1. Polymer matrix/ matrices
2. The drug
3. Pressure sensitive adhesives
4. Permeation enhancers
5. Excipients/ other supportive materials.



1.Polymer matrix:

The polymer is formulated either as a matrix/ reservoir to
controls the release of the drug from the device.

Ideal characters:

1.The polymer molecular weight, glass transition temperature and chemical functionality must allow proper diffusion & release of drug.

2. It should be stable, non reactive with the drug, easily manufactured and fabricated into the desired product.

3. The polymer and its degradation products must be non toxic or non antagonistic to the host.

4. The mechanical properties of the polymer should not deteriorate excessively when the large amount of the active agents are incorporated into it.

- The polymers used in the transdermal drug delivery systems are

1. Natural polymers –

Cellulose derivatives ,zein , gelatin , shellac ,waxes, proteins, gums and their derivatives , natural rubber starch etc.

2. Synthetic elastomers-

Poly butadiene , hydrin rubber , poly siloxane silicone rubber , nitrile , acrylonitrile ,butyl rubber, butadiene Neoprene etc.

3. Synthetic polymers-

Polyvinyl chloride, polyethylene, poly propylene, polyacrylate ,polyamide ,polyurea, polyvinyl pyrrolidone, poly methyl methaacrylate

2. Drug:

For successful development of a transdermal drug delivery, the following are the desirable properties of a drug.

Physicochemical properties.-

It is generally accepted that the best drug candidates for passive adhesive Transdermal patches must be :

- Non-ionic.
- Low molecular weight (less than 1000 Daltons),
- Adequate solubility in oil and water .
- Low melting point (less than 200℃)
- Potent (dose ideally less than 10 mg per day).

Biological properties –

- The drug should be potent with a daily dose of order of
- a few mg/ day.
- The half life of the drug should be short.
- The drug must not induce a cutaneous irritant or allergic response.
- Drugs degraded in the GIT or inactivated by the hepatic first pass are suitable candidates for transdermal drug delivery.
- Tolerance of drug must not be developed.
- Drugs which are to be administered for long period of time or which cause adverse effects are suitable.

3. Pressure sensitive adhesives:

These provide good adherence characteristics & help to secure the transdermal device on the skin over long period of time.

Ideal properties:--

- Should not irritate or sensitize the skin or affect normal functions of the skin
- Should adhere to the skin aggressively
- Should be easily removed
- Should not leave an un washable residue on the skin
- Should have an intimate contact with the skin
- Should be compatible with the drug, excipients and permeation enhancers
- Permeation of drug should not be affected

- The major classes of pressure sensitive adhesives are **Polyisobutylenes, Acrylic & Silicone based adhesives.**

1. Polyisobutylene based adhesives: (Tg = - 62°C)

- These elastomeric polymers are commonly used as primary base polymer and as tackifiers.
- The higher the mol. Wt. of PIB the lower its permeability.
- These are preferred for drugs with low solubility and low polarity.

2. Acrylic adhesives: (Tg = - 55 to - 15°C)

- These are produced by co-polymerization of acrylic esters with acrylic acid and other functional monomers.
- These are used as matrix adhesives and dominate the medical market.

3. Silicone based adhesives: (Tg = - 127°C)

- These are composed of long chain PDMS and benzene soluble silicate resin.
- The unique semi-organic structure give silicone a high flexibility.
- Silicone adhesives have high permeability to moisture and oxygen which reduces degree of occlusion.
- These are suitable for TDDS in which drug releasing surface is covered with adhesive.

4. Permeation enhancers:

- These are the compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant (drug).
- These are also known as accelerants / sorption promoters.

Ideal properties:

1. Should work rapidly.
2. The activity and duration of effect should be both predictable and reproducible.
3. Should not have pharmacological activity.
4. Should work unidirectionally (prevent loss of endogenous material from body).
5. When removed form skin, the barrier properties should return both rapidly and fully

Permeation enhancers act through 3 possible mechanisms;

1. The enhancers disrupt stratum corneum lipid organization, making it permeable & increases drug diffusion coefficient.

Ex: Azone, terpenes, fatty acids, DMSO and alcohols.

- Oleic acid and terpenes at high loadings pool with lipids, phase separate and form permeable pores which allow easier access to the viable epidermis for polar molecules.
- DMSO, ethanol and micellar solutions also extract lipids making horny layer more permeable by forming aqueous channels.

2. The enhancers interact with keratin (intra cellular protein) in corneocytes to open up dense protein structures and make them more permeable.
Ex: Ionic surfactants, decyl methyl sulphoxide and DMSO
3. Many solvents enter stratum corneum, changes its solution properties by altering the chemical environment and increasing partitioning of second molecule (drug/ co-enhancer/ co-solvent) in to the horny layer.
Ex: ethanol increases penetration of nitroglycerin & estradiol.

- Many chemical enhancer use combination of 3 mechanisms. DMSO (above 60%) disturb inter cellular organization, extract lipids & interact with

- Permeation enhancers act on skin to improve drug diffusibility / solubility / both.
- DMSO and azone can increase diffusability in the stratum corneum by acting as solvents to dissolve the skin lipids and to denaturate skin proteins.
- Ethanol, macrocyclic ketones, lactones can modify drug solubility parameters, partition coefficient from vehicle to skin and the permeability coefficient in the skin.

1. Solvents

- Increases penetration by swelling the polar pathway transport or fluidising lipids
  Eg: water, ethanol, methanol, DMS, homologs of methyl
  sulphoxide, dimethyl acetamide and DMF, 2-pyrrolidone, Nmethyl, 2-pyrrolidone, laurocapram, PG, glycerol, silicone fluids, isopropyl palmitate.

2. Surfactants

- Enhances the polar pathway transport of hydrophilic drugs.
- Anionic surfactants can penetrate and interact strongly with the skin, cationic surfactant are irritants.

a. Anionic surfactants: Dioctyl sulpho succinate, SLS, deco

b. Non ionic surfactants: Pluronic F127, Pluronic F68,etc.

c. Bile salts: Sodium taurocholate, sodium deoxy cholate, sodium tauroglycocholate.

3. Binary systems

- These open heterogeneous mualti laminate pathway continuous pathways.
- Propylene glucol-oleic acid and 1,4-butane diol-linoleic acid.

4. Miscellaneous

- Urea-hydrating and keratolytic agent, N,N-dimethyl-mtoluamide,calcium thioglycolate, anti cholinergic agents

5. Potential permetion enhancers

5. Excipients/ other supportive materials.

These include **Release liners, Backing layers, Microporous membranes & Packing substrates.**

1. **Release liner:**

- During storage the patch is covered by a protective liner that is removed & discharged immediately before the application of the patch to the skin.
- The release liner should be capable of easily peeled off by the user and should not interfere with the functionality of the product.
- It prevents loss of drug that has migrated through adhesive layer during storage and protects product against contamination.
- Cost must be compatible with a disposable concept as loner will be thrown away.

2. Backing layer:

- Flexible and provide good bond to the drug reservoir
- Prevent drug from leaving the dosage form from the top.
- Accept printing
- Should be impermeable to water vapor.

  E.g. metallic plastic laminate, plastic backing with absorbent pad and occlusive base plate, adhesive foam pad with occlusive base plate.
- Materials used:-- polyester-polyethylene coextruded films.

3. Microporous or semi-permeable or rate controlling membrane:

- These are used to limit the flow of the drug from both reservoir and matrix systems.
- The function depends on the design of the specific system, the size of the active component and the need to have a rate-limiting factor in order to satisfy the release and absorption characteristics of the system. Ex: Ethylene Vinyl Acetate Membranes (EVA), Microporous Polyethylene Membranes.

4. Packing substrates:

- Transdermal patches are packed as unit doses in sealed pouches.
- The pouching material is critical for stability & integrity of product.
- The structure and construction of film pouch depends on product characteristics, reactivity and adsorption phenomena of drug and external factors (light, oxygen)

  Three main layers used for pouches:

  1. External printable layer.
  2. Aluminum foil layer
  3. Internal plastic heat sealable layer

FACTORS AFFECTING TRANSDERMAL PERMEATION

Physicochemical property of Drug molecule,

- Partition co-efficient,
- pH Condition,
- Drug Concentration,
- Molecular weight.
  Physicochemical property of Drug Delivery System,
- Release characteristics,
- Use of permeation enhancer,
- Composition of Drug Delivery System.

Pathophysiological condition of Skin,

- Reservoir effect of Horney Layer,
- Hydration of skin,
- Lipid Film,
- Skin Temperature,
- Pathological Injury to Skin,
- Regional variation.

Transdermal patch

- A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a time-released dose of medication through the skin and in to the bloodstream.
- Currently patches are used in several **therapeutic areas** including pain management, smoking cessation, treatment of heart disease, hormone replacement and management of motion sickness.

  Types of TDDS / Approaches in development of TDDS:

  1. Membrane permeation controlled systems / Reservoir type systems.

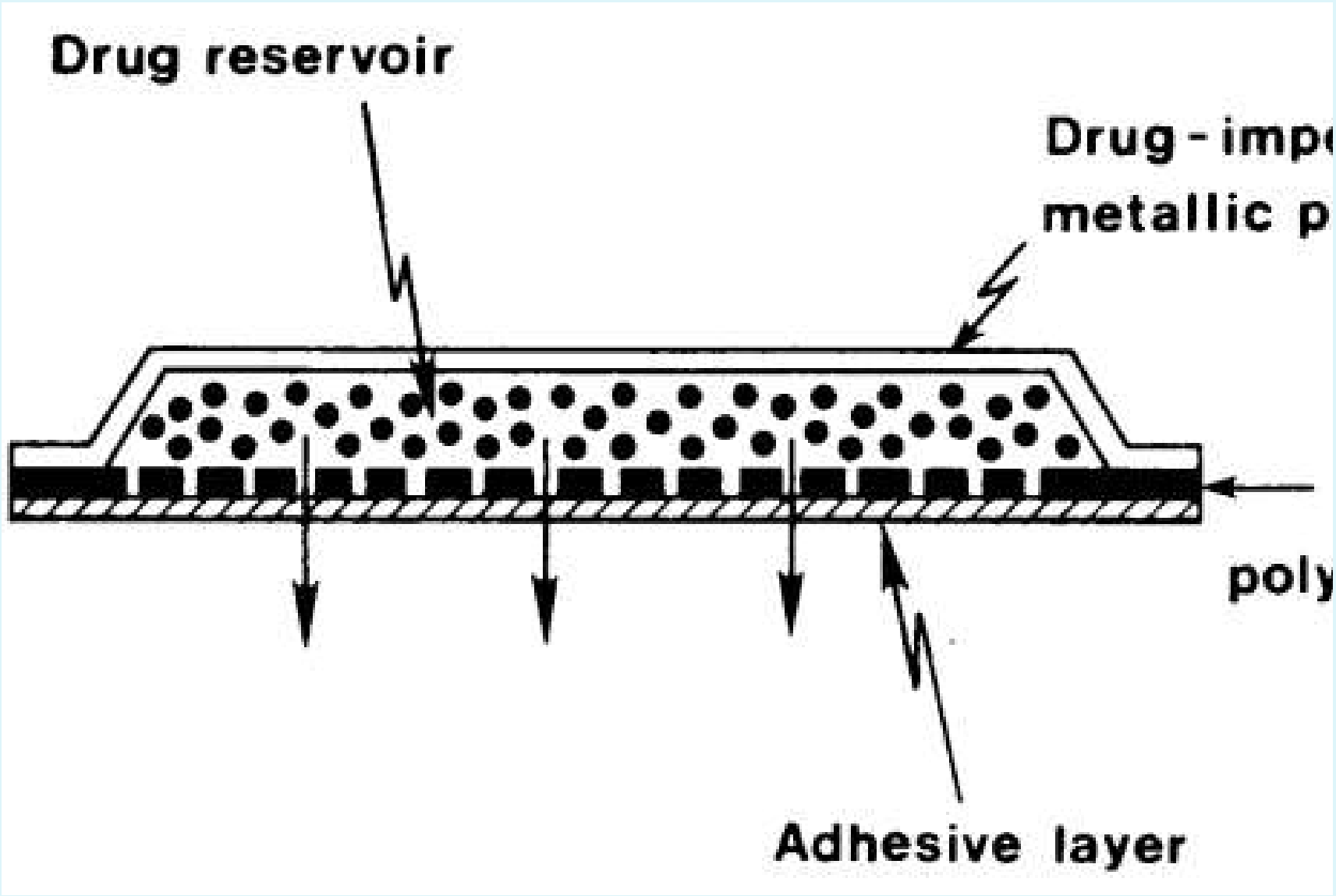
  2. Adhesive- dispersion type systems.

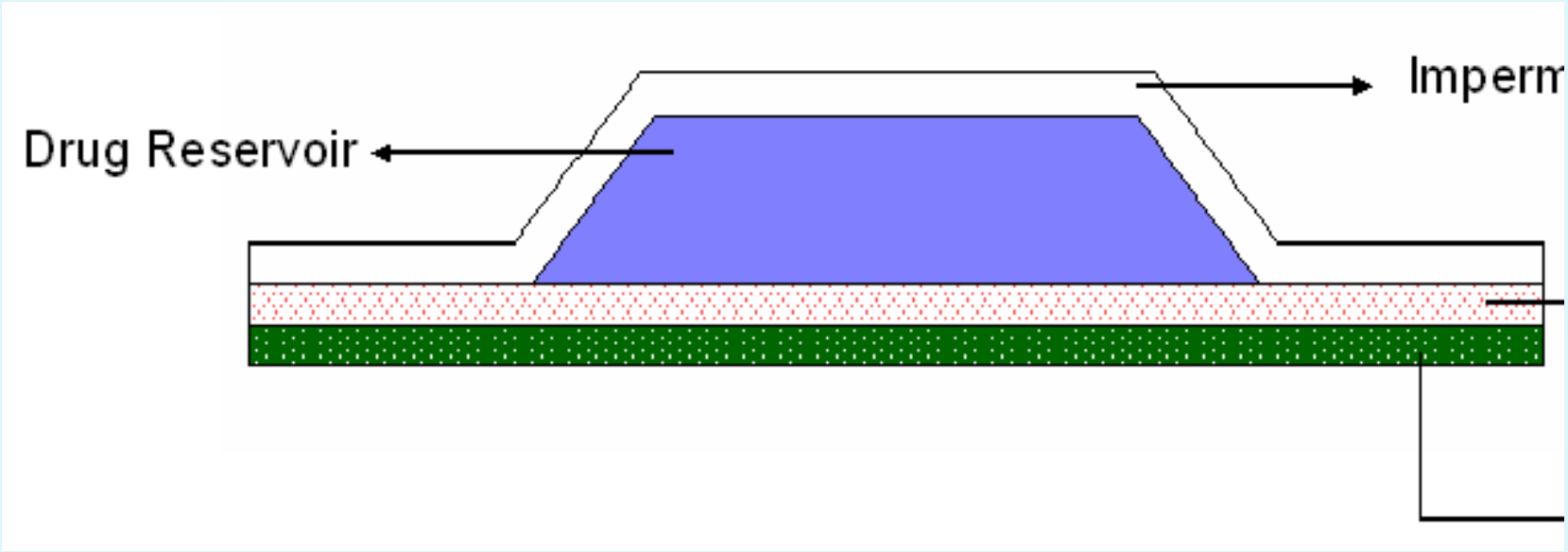
  3. Matrix diffusion- controlled systems.

  4. Microreservoir type/ microsealed dissolution controlled systems.

1.Membrane-moderated or Permeation controlled TDDS (Reservoir type)

- Drug reservoir (homogenous dispersion of drug with polymeric matrix or suspension of drug in un leachable viscous liquid medium such as silicone fluid) is encapsulated within drug impermeable metallic plastic laminate and a rate controlling polymeric membrane (ethylene vinyl acetate co polymer)
- The rate of drug release is determined by the permeability of the rate controlling membrane.
- A layer of **adhesive polymer is applied on membrane to** secure the device on skin.
- The rate of release of drug is always maintained at constant rate & the type of release is **zero order.**


Drug reservoir
Drug - impe
metallic p
poly
Adhesive layer

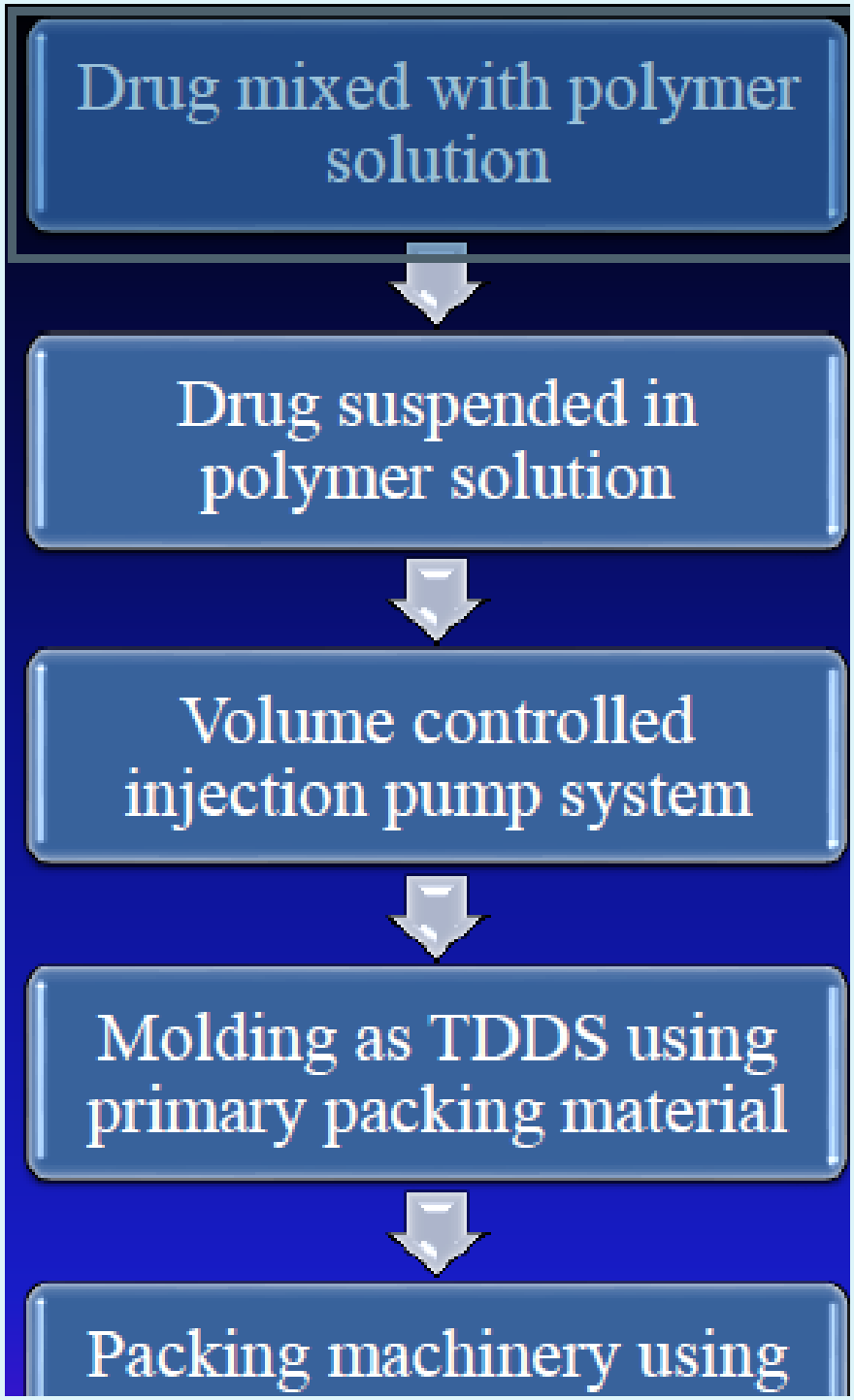


- TransdermScop® (Scopolamine) for 3 days protection of motion sickness.
- The drug reservoir is encapsulated in a shallow compartment moulded from drug impermeable metallic – plastic lamination whilst the drug delivery side is covered by controlling polymeric membrane.

- A thin layer of silicone or poly acrylate adhesive may be applied to the external surface of the rate controlling membrane to achieve intimate contact of the TDDS and the skin surface
- Release rate of this TDDS depends upon the polymer composition, permeability co efficient and thickness of the rate controlling membrane and adhesive
- The intrinsic rate of drug release from this TDDS is calculated by the following formula

$$\frac{dQ}{dt} = \frac{CR}{1/Pm + 1/Pa}$$

- CR-con.of drug in the reservoir compartment
- Pm-permeability co efficient of rate controlling polymeric
- membrane
- Pa- permeability co efficient of adhesive


Drug mixed with polymer solution
Drug suspended in polymer solution
Volume controlled injection pump system
Molding as TDDS using primary packing material
Packing machinery using

Example of this system are

1.Nitro glycerin releasing TDDS (Transderm-Nitro/ciba,USA)for once a day medication in angina pectoris

2.Scopolamine releasing TDDS (Transderm-Scop/ciba,USA)for 72 hrs.prophylaxis of motion sickness

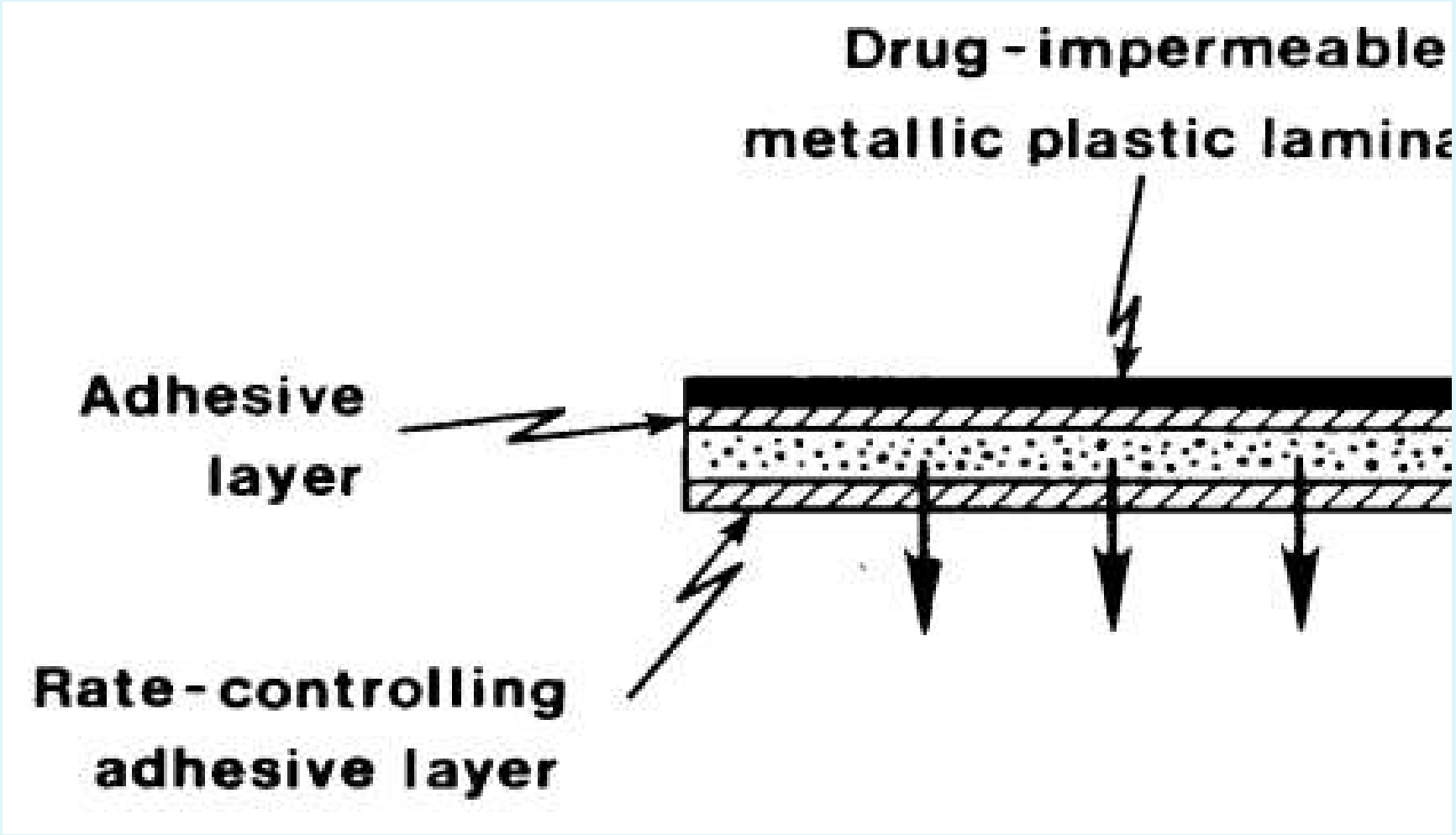
3.Estradiol releasing TDDS (Estraderm/ciba)for treatment of menopausal syndrome

4.Clonidine releasing TDDS (Catapres/Boehringer Ingelheim)for 7 day therapy of hyper tension

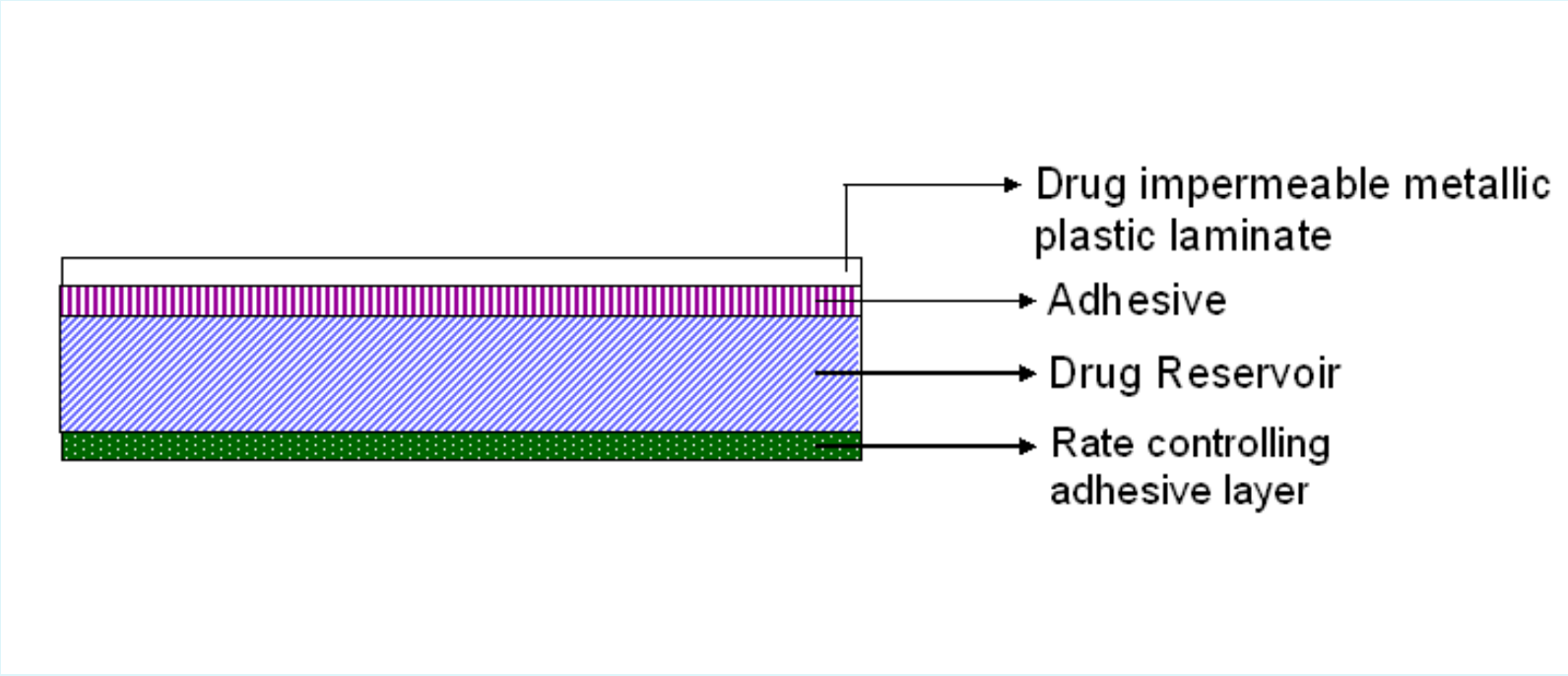
5. Prostaglandin-derivatives TDDS

2.Adhesive diffusion/dispersion controlled TDDS

- Drug reservoir – homogenous dispersion of drug with adhesive polymer (poly(isobutylene) or poly acrylate)
- Then spreading of this medicated adhesive polymer on flat sheet of drug impermeable metallic plastic backing to form thin drug reservoir layer
- On top of the drug reservoir layer, thin layers of rate controlling adhesive polymer of specific permeability and constant thickness are applied to produce an adhesive diffusion/dispersion-controlled TDDS


Drug-impermeable
metallic plastic lamina
Adhesive
layer
Rate-controlling
adhesive layer

- It is the simplified form of membran moderated drug delivery system
- It is prepared by directly dispensing the drug in an adhesive polymer & then spreading the medicated adhesive by solvent film casting method over a flat sheet of drug impermeable metallic or plastic backing membrane, this forms a thin drug reservoir layer.



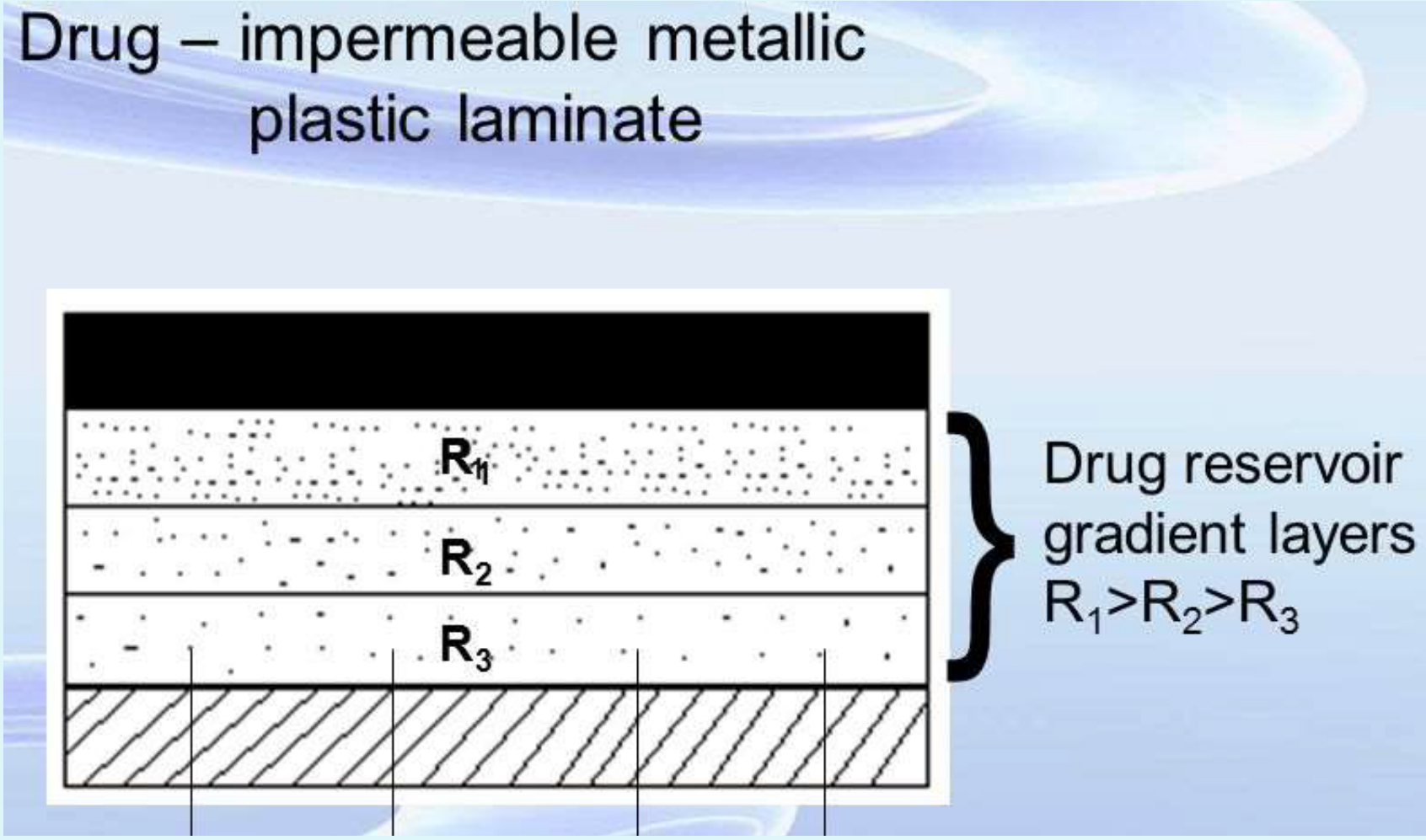
Deponit® (Nitroglycerine) for once a day medicatin of angina pectoris

- The rate of drug release in this system is defined by

$$\frac{dQ}{dt} = \frac{Ka/r.Da}{ha} cR$$

- Where
- Ka/r-partition co-efficient of drug bw adhesive layer and reservoir layer
- Da-diffusion co-efficient of drug in the adhesive layer
- ha-thickness of adhesive layer
- Examples for this system
  1.Iso sorbide dinitrate-releasing TDDS
  2.Verapamil releasing TDDS

- Alternatively, this type of TDDS can be modified to have the drug loading level varied by increment to form **gradient of drug reservoir along the multi laminate adhesive layers.** Ex: **Nitroglycerine releasing TDDS**

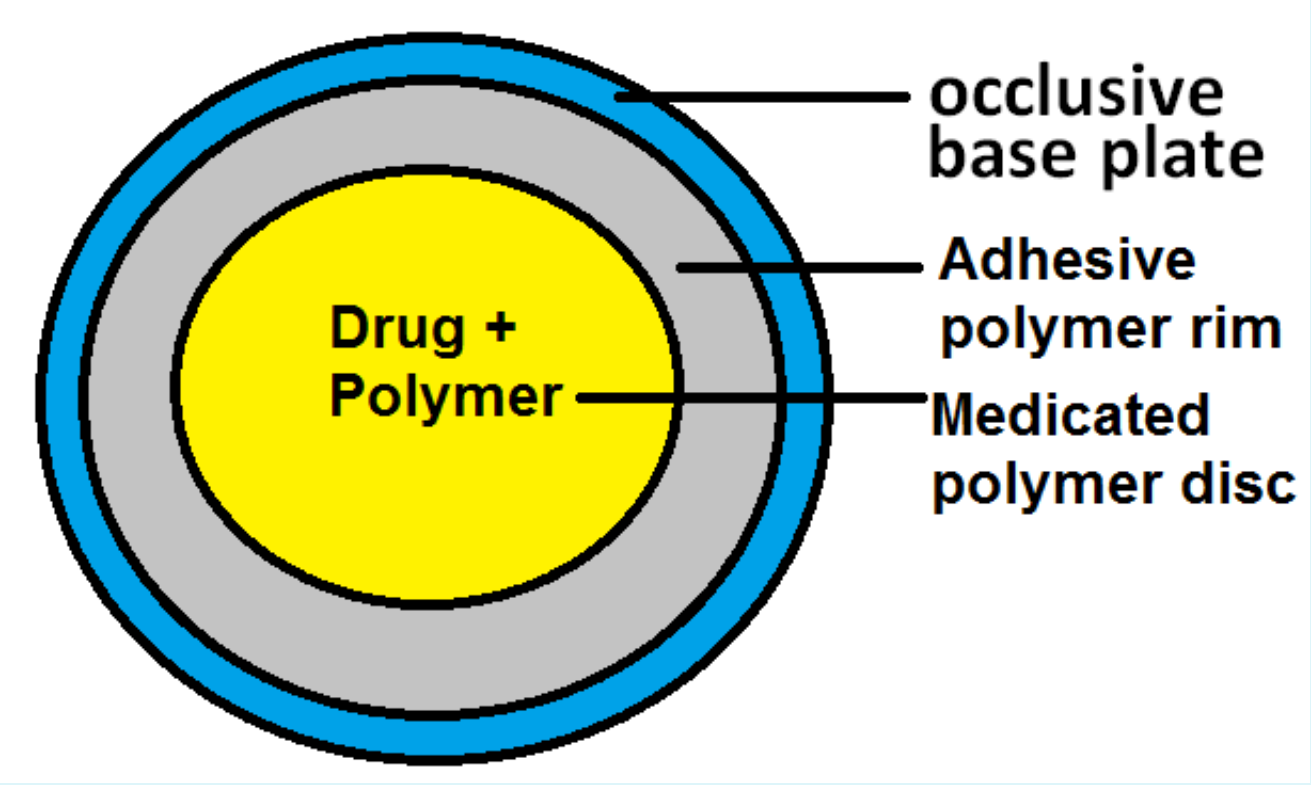


3.Matrix diffusion-controlled TDDS

Drug reservoir

- Homogenous dispersion of drug with hydrophilic or lipophilic polymer matrix by any one of the following methods
- Homogenous dispersion of finely ground drug particles with liquid polymer or highly viscous base polymer followed by cross linking of polymer chains
- Homogenous mixing of drug solid with rubbery polymer at an elevated temperature
- Dissolving the drug and polymer in a common solvent followed by solvent evaporation in a mould at an elevated temperature or under vacuum.
- Medicated polymer is moulded in to desired surface area and controlled thickness
- This medicated polymer disc is pasted on to an occlusive base plate with impermeable plastic backing
- Then the adhesive polymer is spread along the circumference to form a strip of adhesive rim around the medicated disc

- The **advantage of this TDDS is absence of dose dumping** as the polymer cannot rupture



Example of this system

1.Nitro glycerin releasing TDDS (Nitro-Dur and Nitro-Dur II /Key pharmaceuticals,USA) deliver daily dose of 0.5mg/cm2 for therapy of angina pectoris.

- The **rate of drug release from this system is defined as**

$$dQ / dt = \{A\ Cp\ Dp / 2t\}1/2$$

where

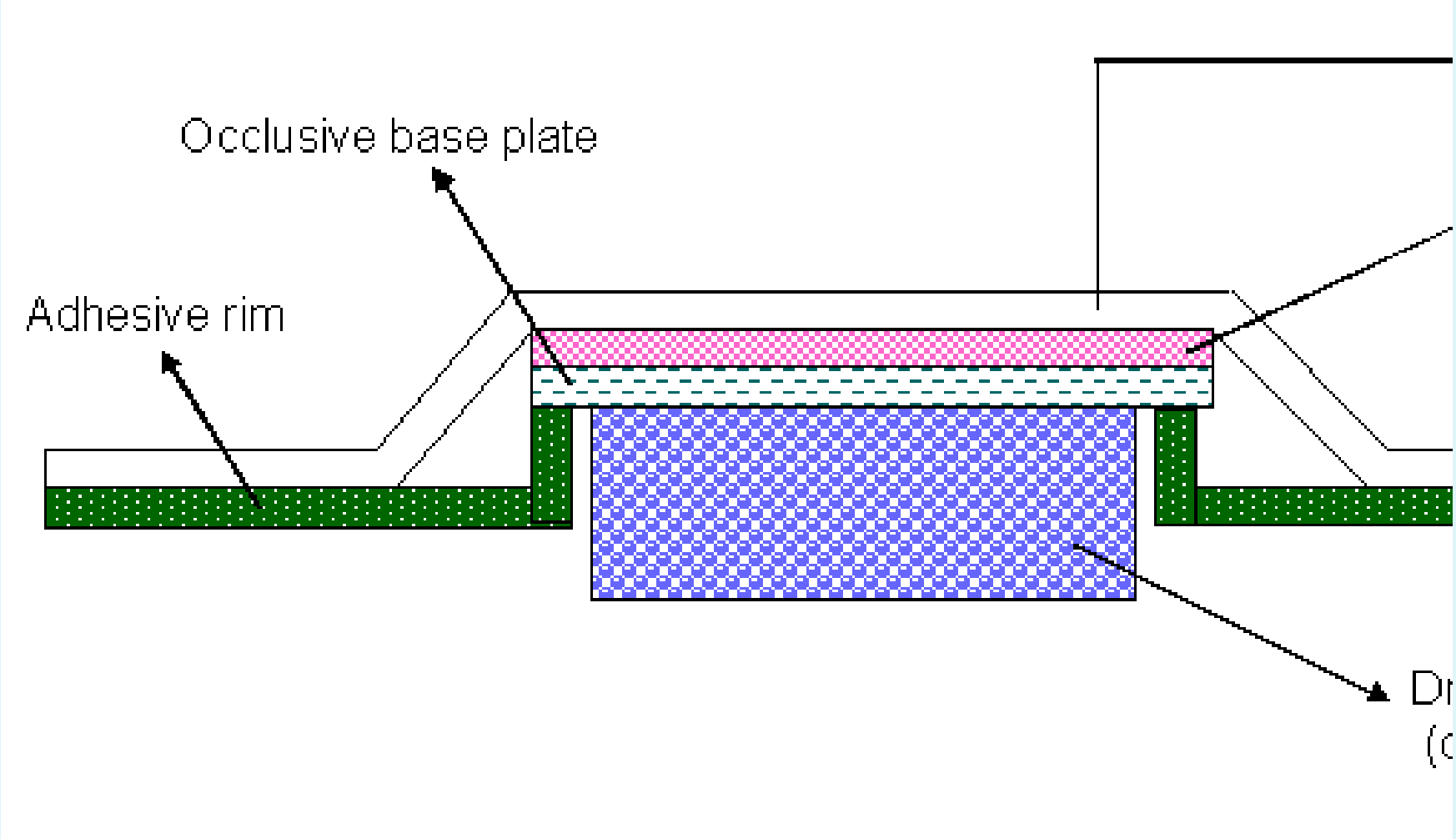
- A- initial drug loading dose in polymer
- Cp and Dp are solubility and diffusivity of drug in polymer matrix.

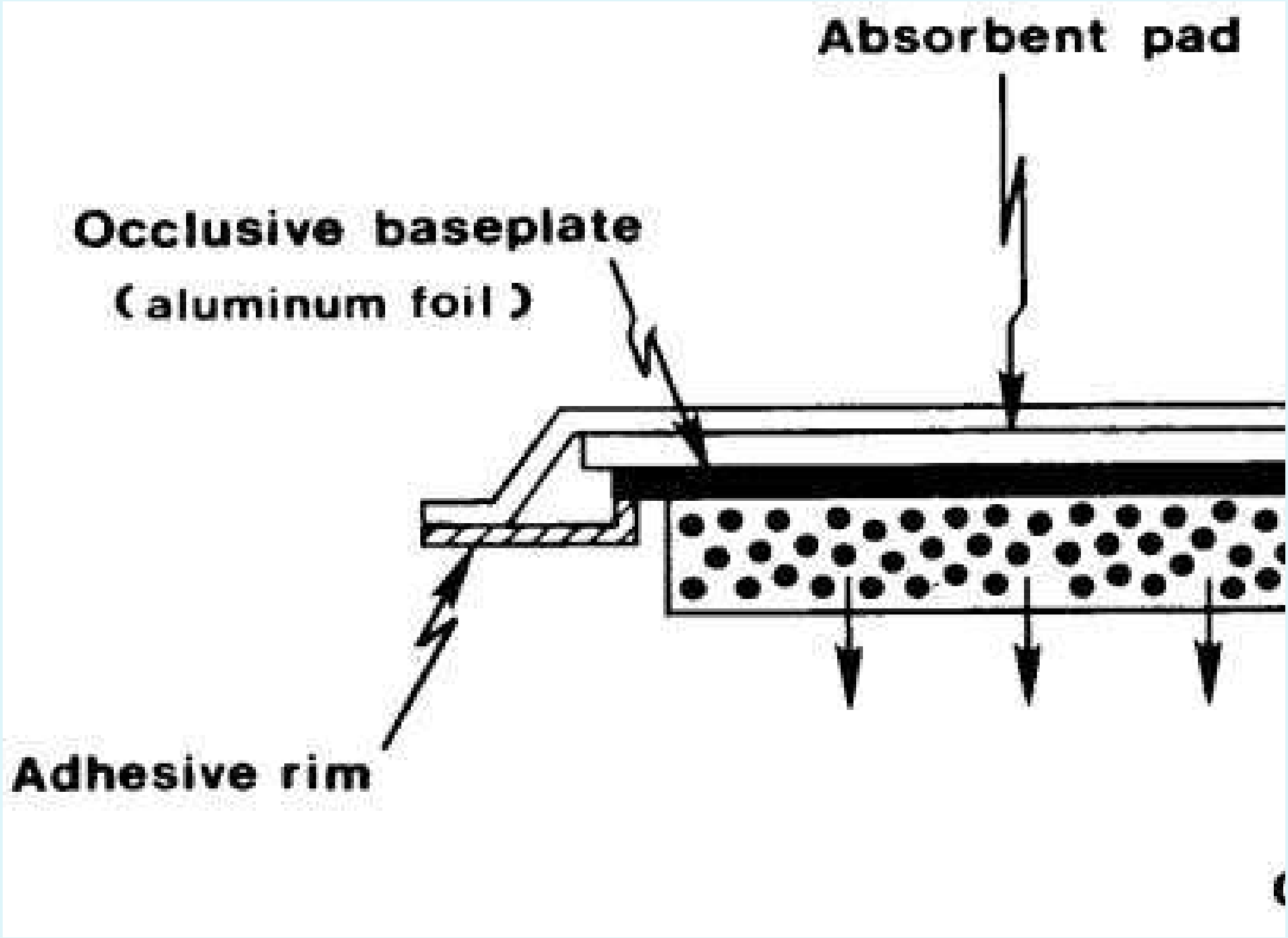
- The rate of drug release from this system at steady state is defined as

$$Q/t1/2= [(2A-Cp)\ Cp\ Dp]\ 1/2$$

2. Estradiol di acetate releasing TDDS
3. Verapamil releasing TDDS

Nitro Dur® (Nitroglycerine) used for once a day medication of angina pectoris.




Absorbent pad
Occlusive baseplate
(aluminum foil)
Adhesive rim

4.Micro reservoir type/micro sealed dissolution- controlled TDDS

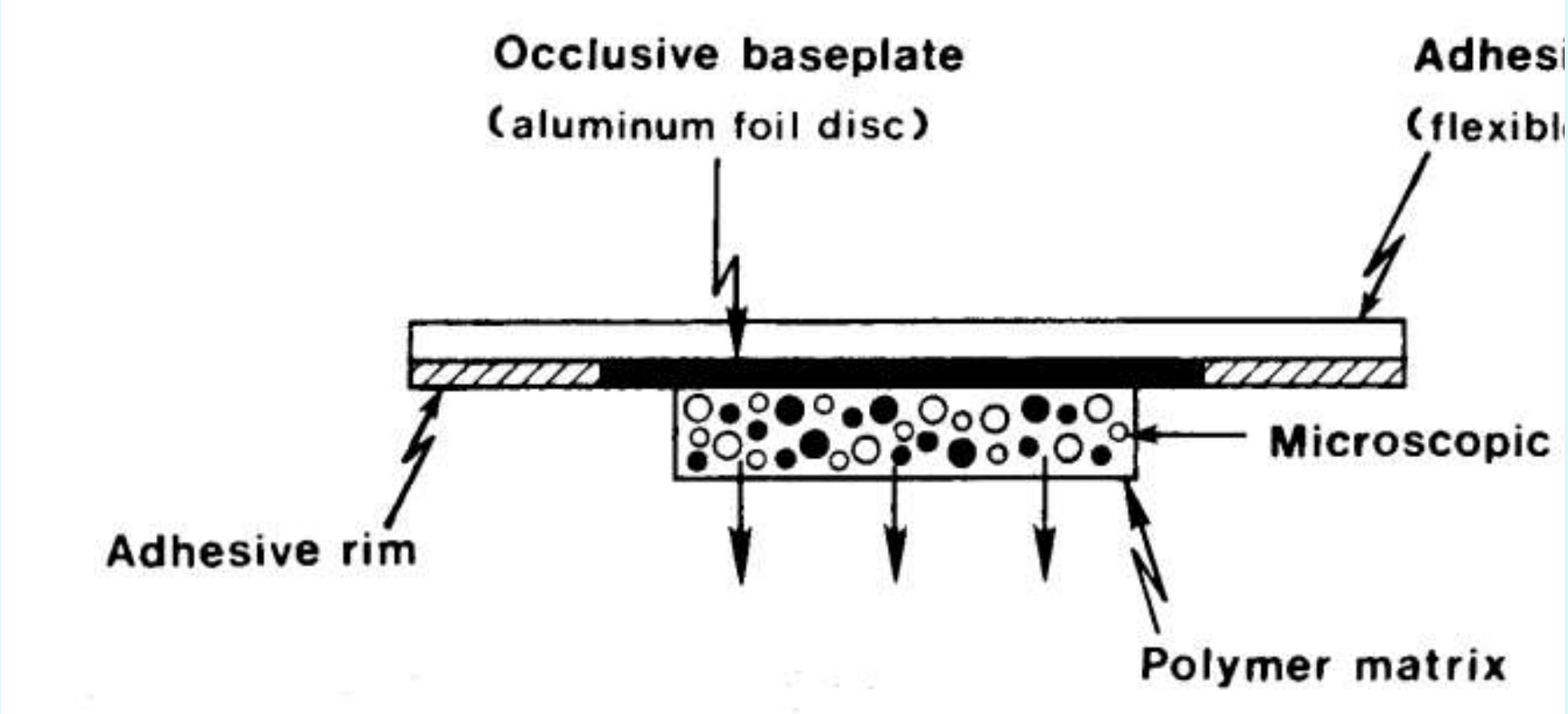
- Combination of the reservoir and matrix diffusion
  Drug reservoir
- Suspension of drug with aqueous solution of water soluble liquid polymer
- Homogenous dispersion of drug suspension in a lipophilic polymer(silicone elastomer)
- As a result discrete un leachable microscopic spheres of drug reservoir is formed which is stabilized by cross linking
- Medicated polymer is moulded in to desired surface area and controlled thickness and it is coated with a layer of bio compatible polymer to modify mechanism and rate of drug release
- This medicated polymer disc is pasted on to an occlusive base plate with impermeable plastic backing
- Then the adhesive polymer is spread along the circumference to form a strip of adhesive rim around the medicated disc

Example of this system are

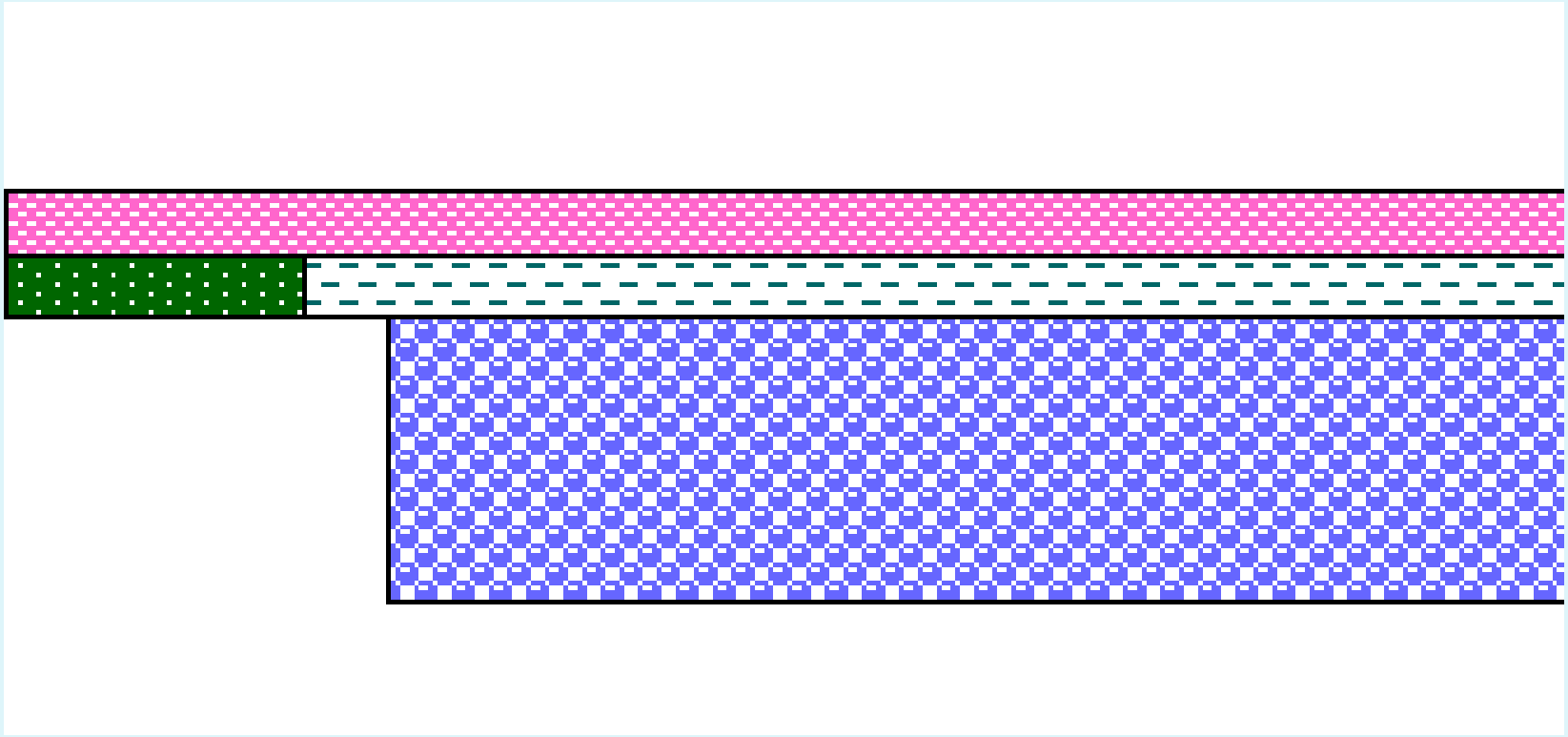
1.Nitro glycerin releasing TDDS (Nitro-Dur and Nitro-Dur II /Key pharmaceuticals,USA)

2. Estradiol di acetate releasing TDDS

3. Verapamil releasing TDDS



Nitro-dur® System (Nitroglycerin) for once a day treatment of angina pectoris.



METHODS FOR PREPARATION

1.Membrane Permeation – Controlled Systems

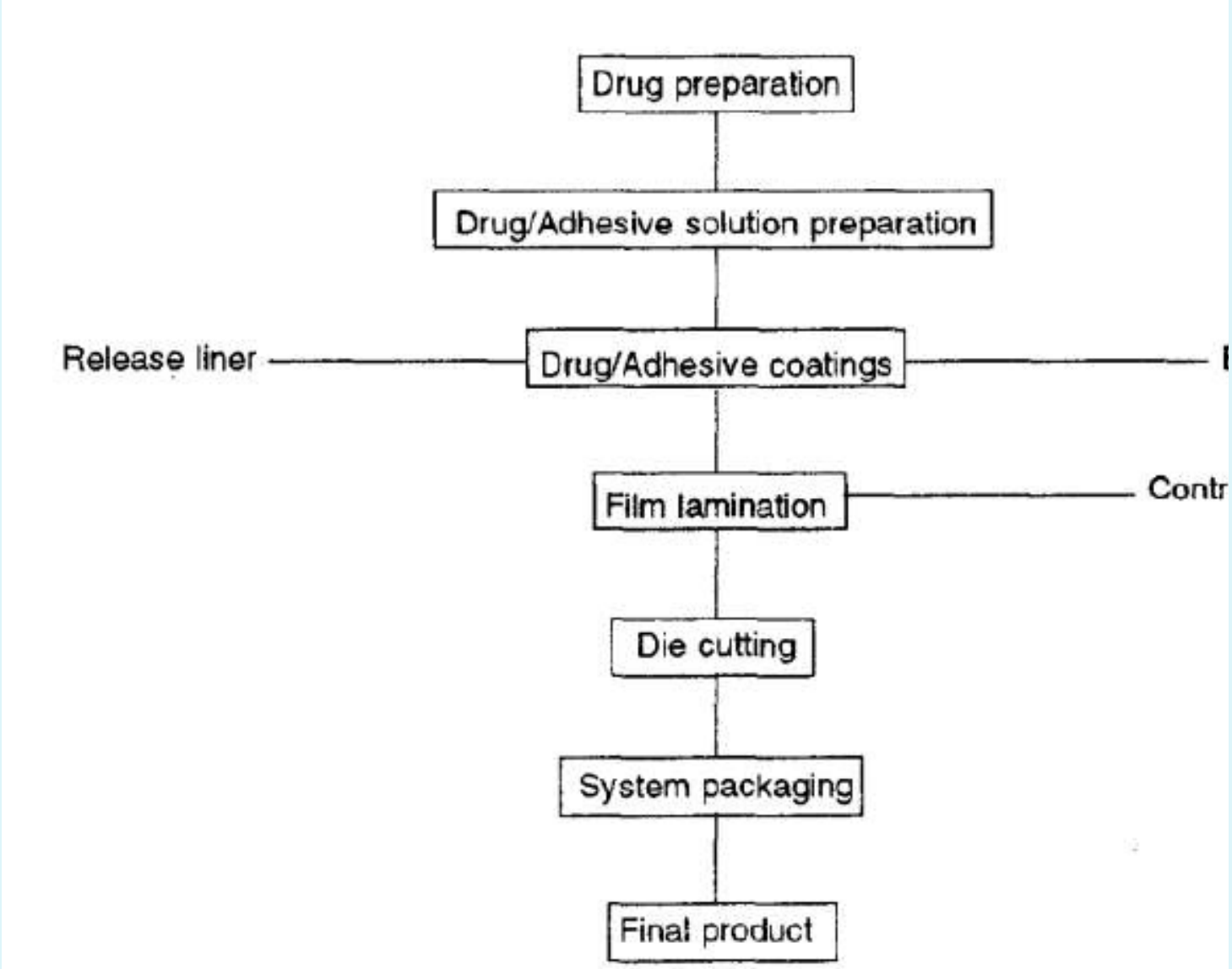


Fig. 5.8. Multilaminate transdermal dosage form manufacturing process flow diagram.

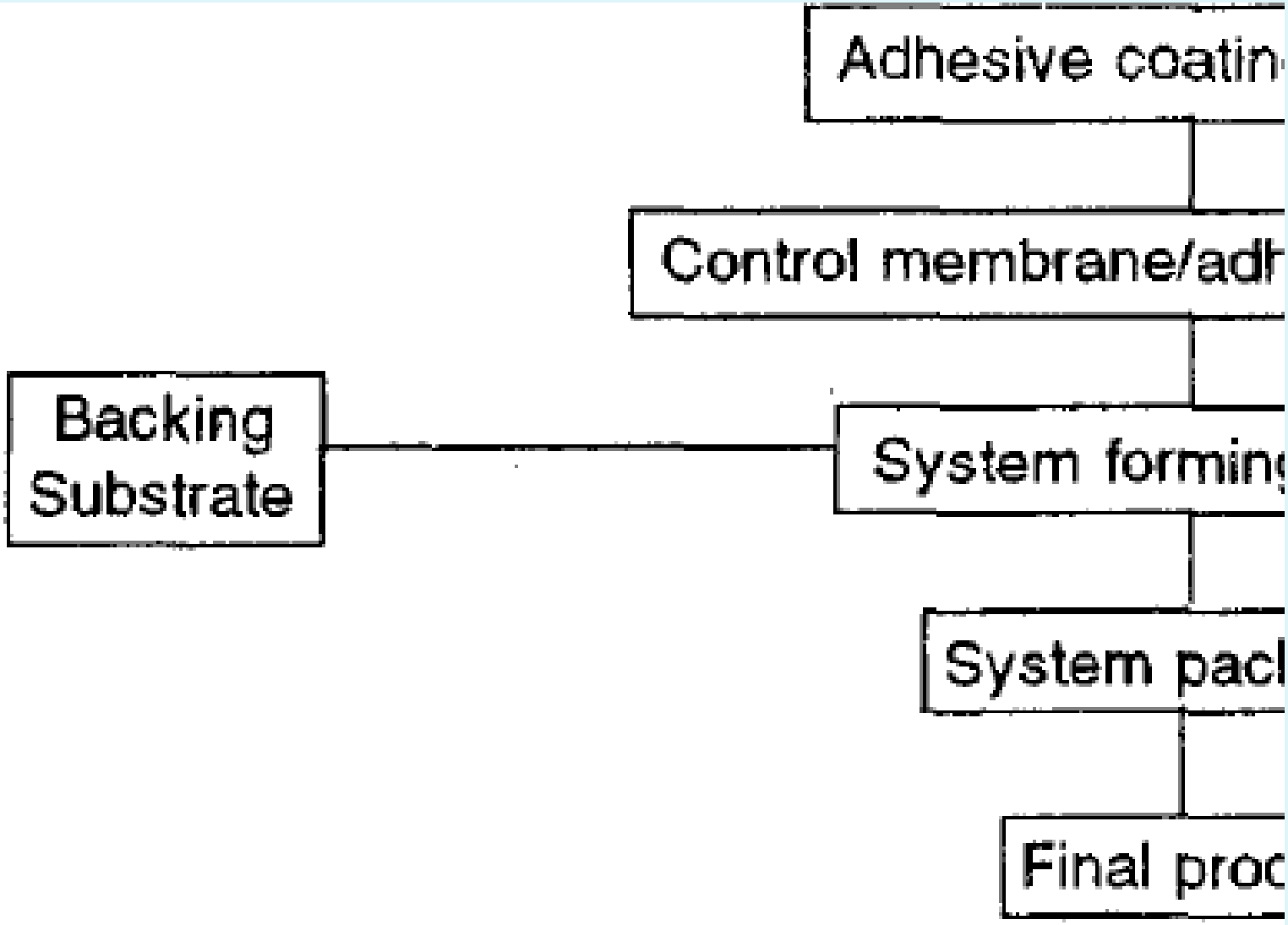


Fig. 5.9. Form-fill-seal proc

Adhesive dispersion – type systems.

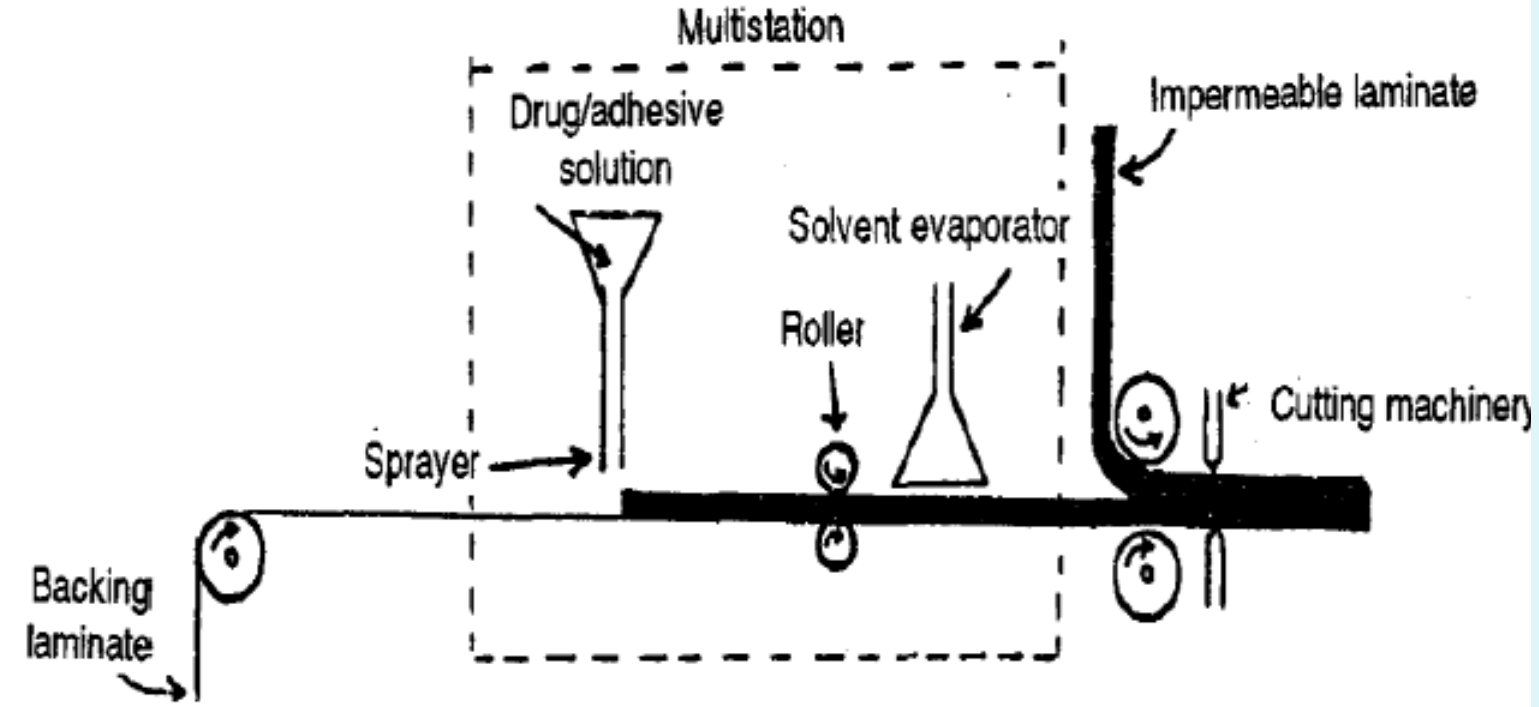
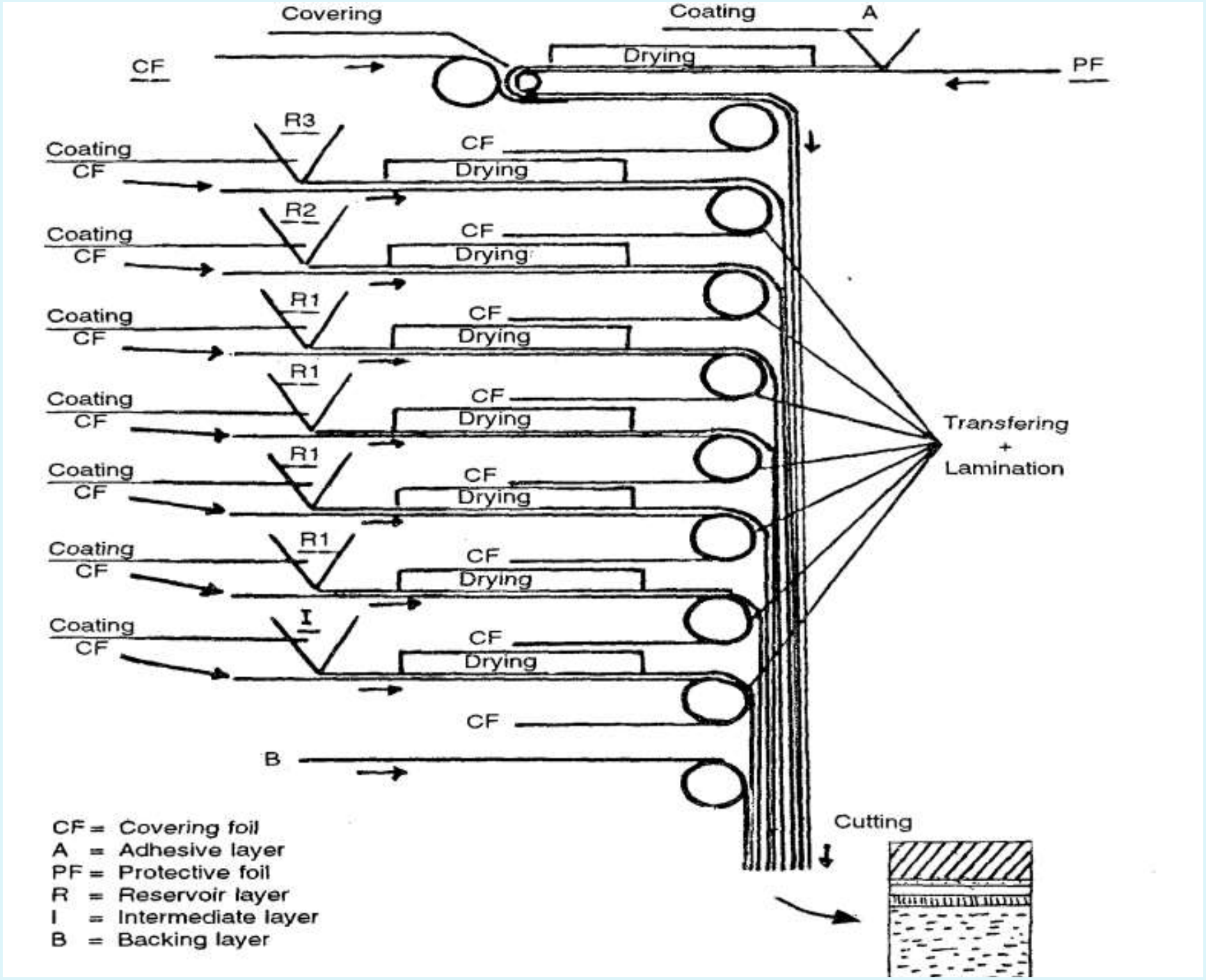


Fig. 5.10. Schematic illustration of the process and equipment involved in the manufacture of an adhesive disp type transdermal therapeutic system.


Covering
Coating
A
CF
Drying
PF
R3
Coating
CF
CF
Drying
R2
Coating
CF
CF
Drying
R1
Coating
CF
CF
Drying
R1
Coating
CF
CF
Drying
R1
Coating
CF
CF
Drying
R1
Coating
CF
CF
Drying
I
Coating
CF
CF
Drying
CF
B
Transfering
+
Lamination
Cutting
CF = Covering foil
A = Adhesive layer
PF = Protective foil
R = Reservoir layer
I = Intermediate layer
B = Backing layer

Matrix diffusion – controlled systems

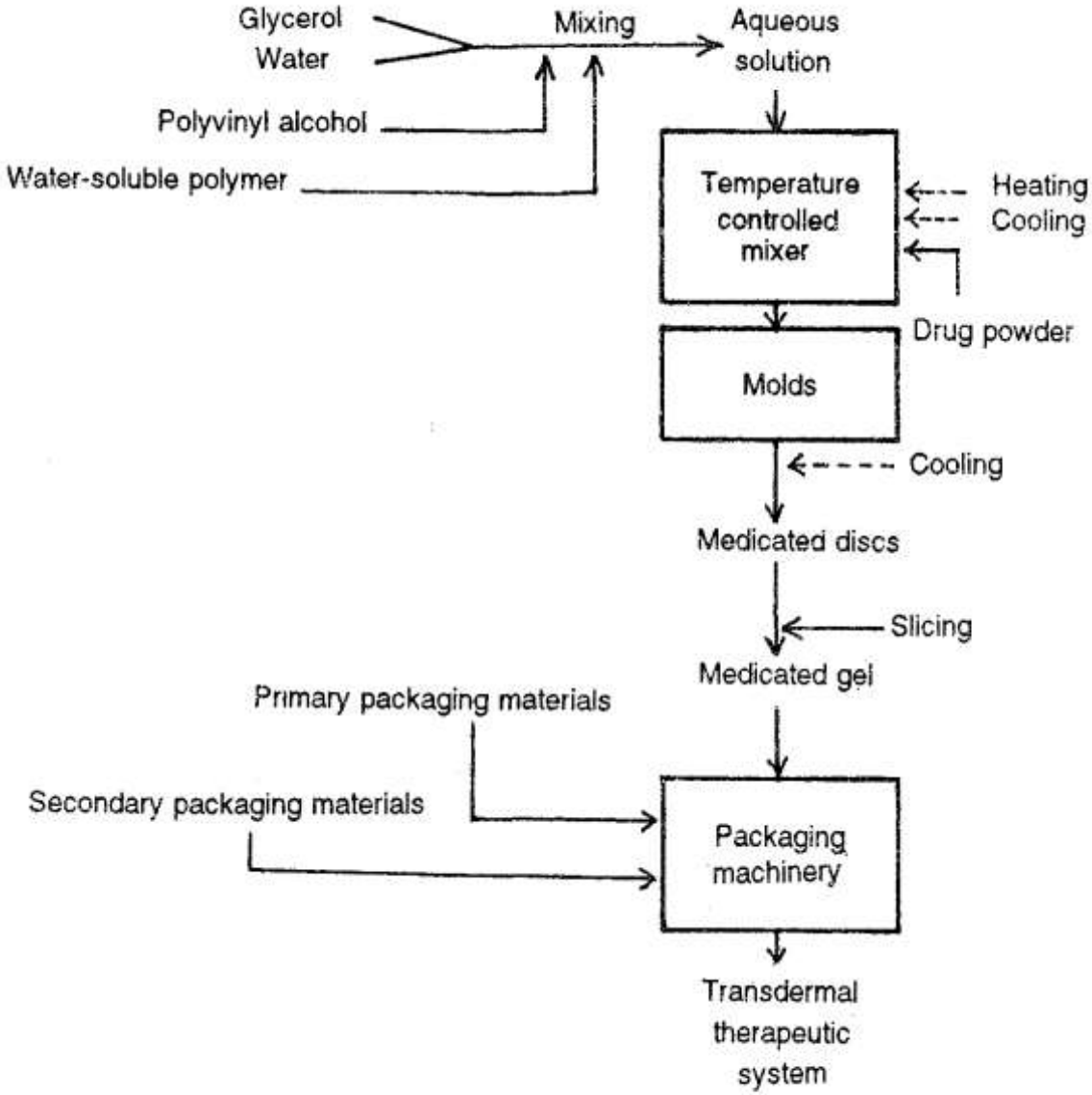
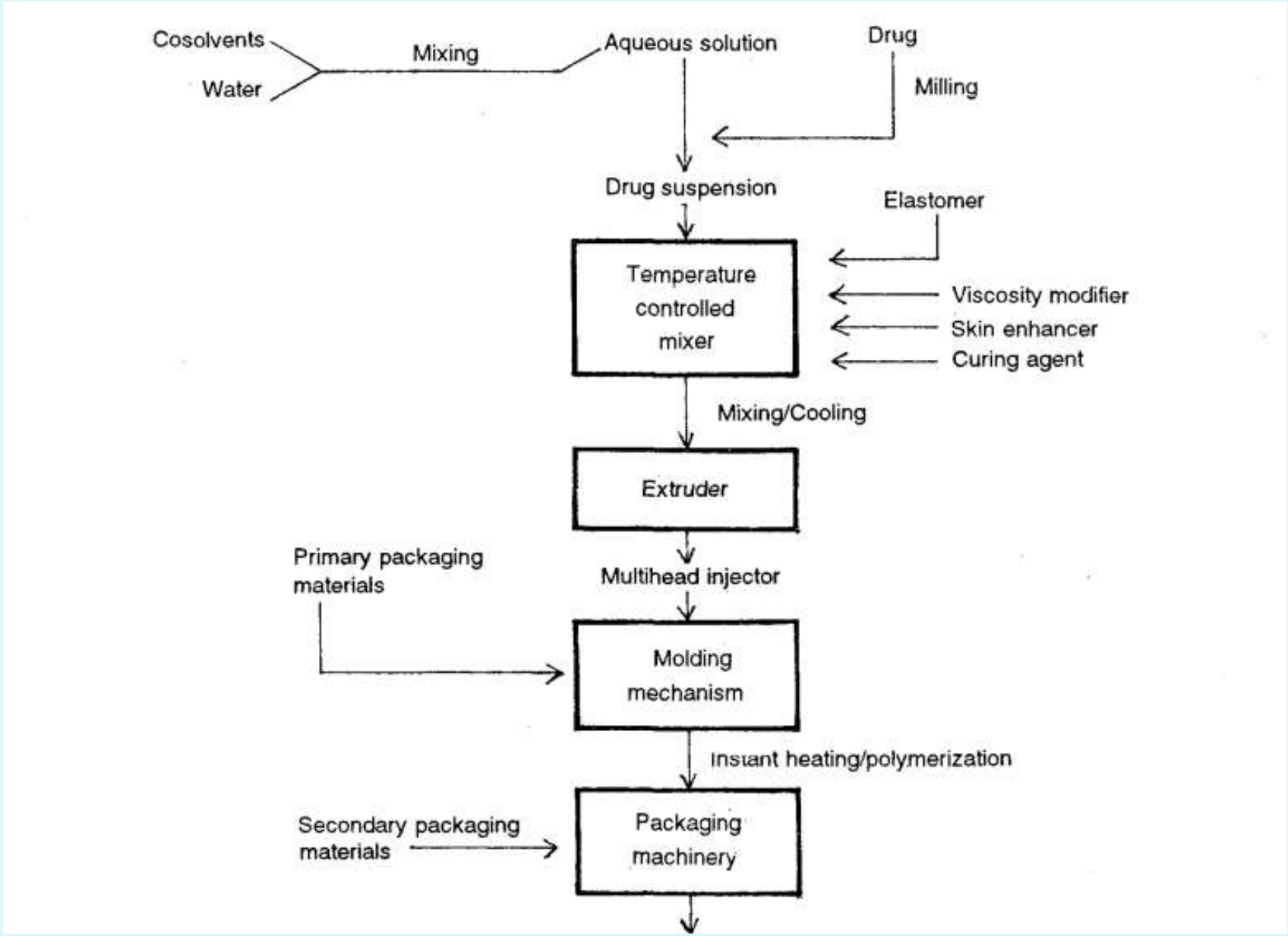
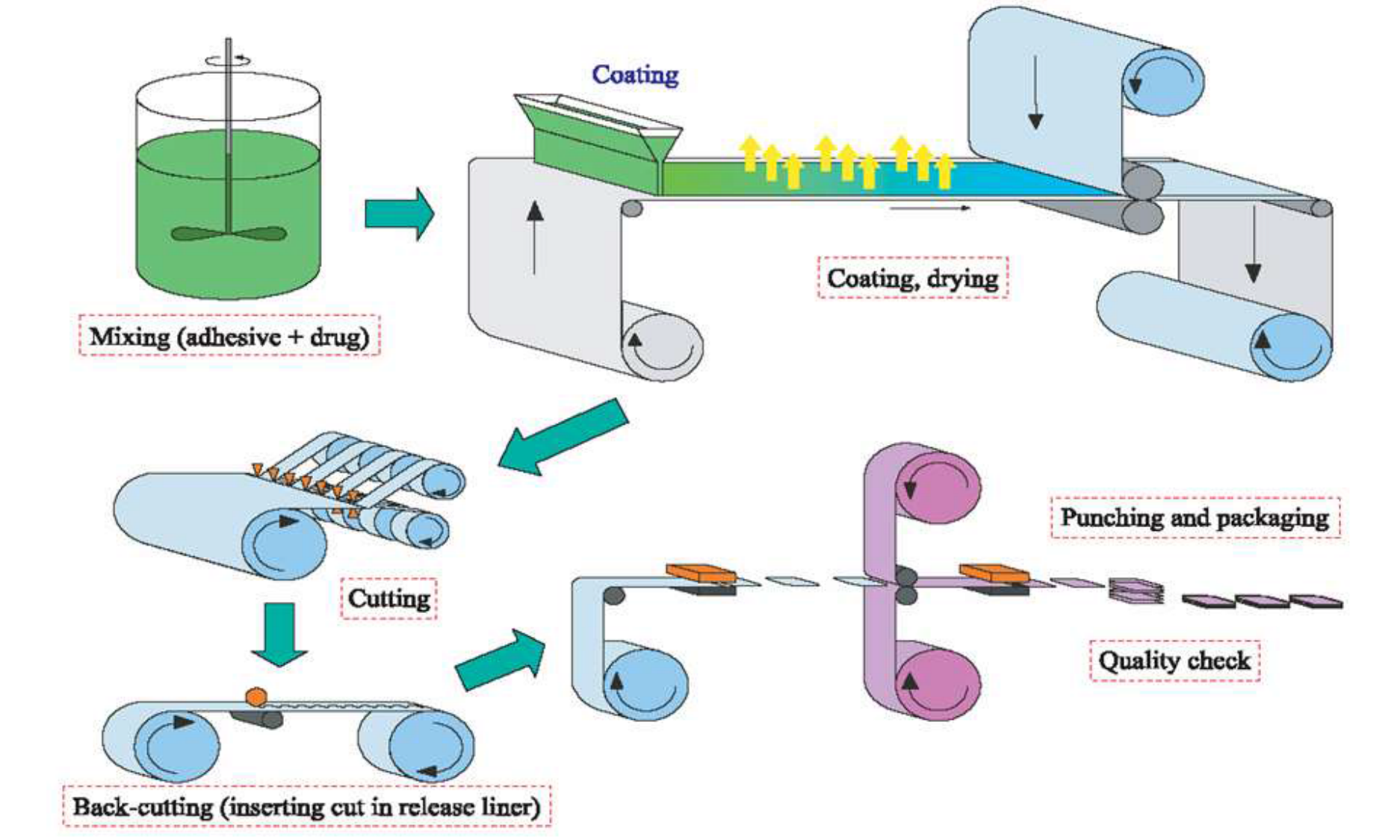


Fig. 5.12. Schematic illustration of the process and equipment involved in the manufacturing of the Nitro-dur

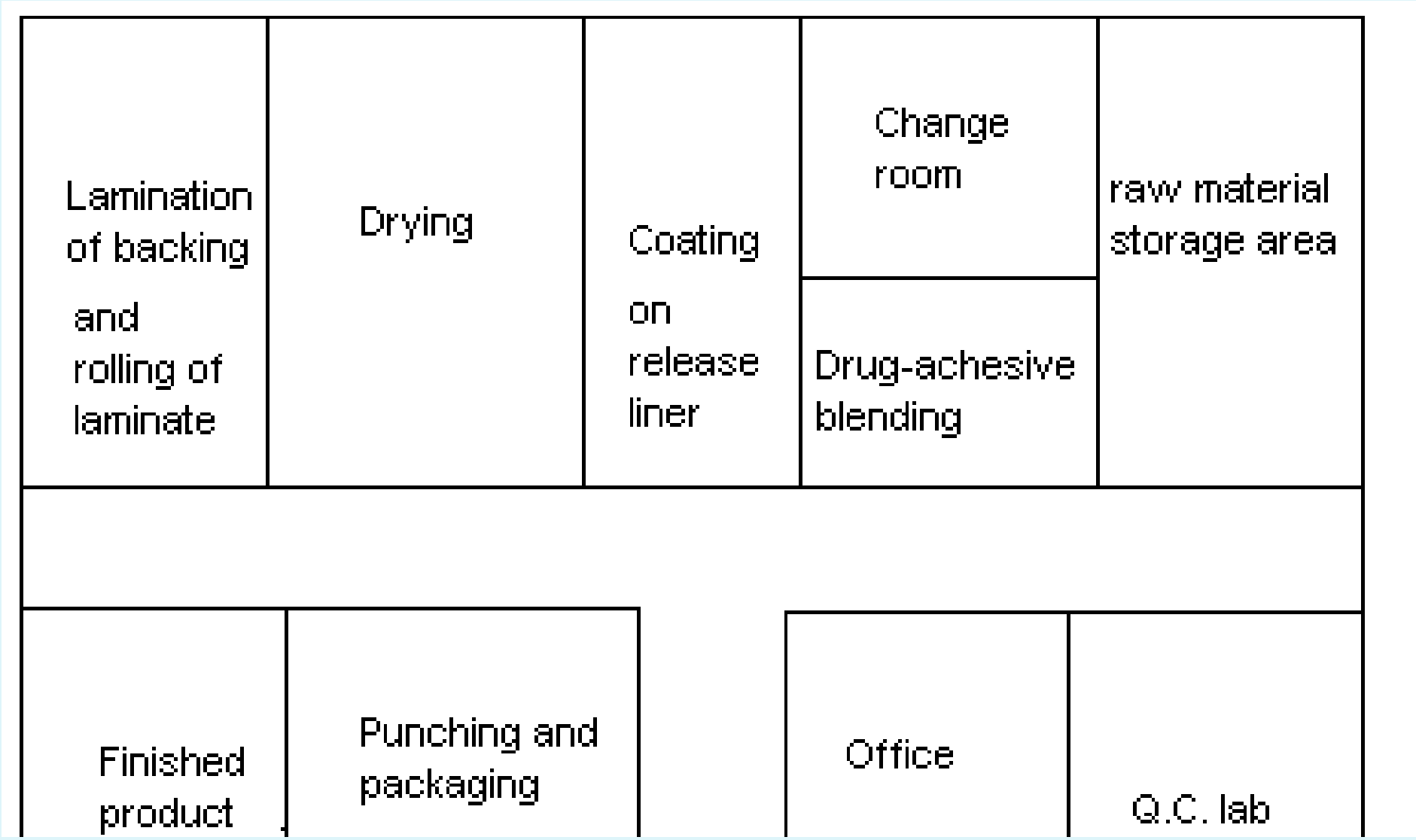
Micro reservoir type or micro sealed dissolution controlled systems.



DESINGING OF TDDS / PREPARATION OF TRANSDERMAL PATCH FROM INDUSTRIAL POINT OF VIEW



Lay out


Lamination of backing and rolling of laminate
Drying
Coating on release liner
Change room
raw material storage area
Drug-achesive blending
Finished product
Punching and packaging
Office
Q.C. lab

EQUIPMENTS

Equipment (Drug in adhesive)

- Mixer
- Drier (explosion proof)
- Coater-laminator
- Slitter
- Die-cutting
- Pouching equipment

Equipment (Drug in reservoir)

- For-fill-seal
- Lamination
- Die-cutting
- Pouching
- Adhesive layer may be preformulated (mixing, drying, lamination)

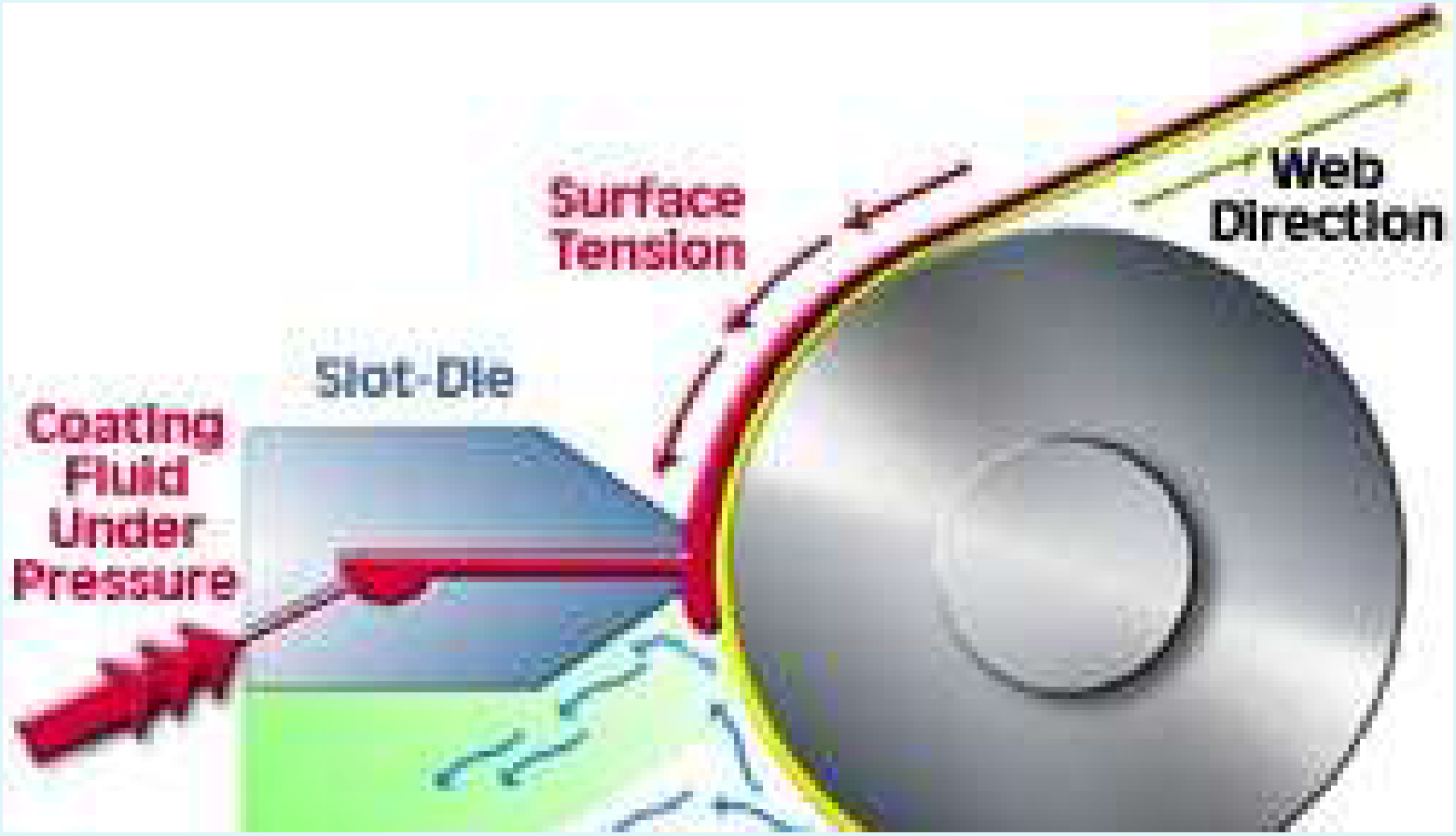
Manufacturing steps

1. Blending

•The first step in manufacturing a patch is blending, where active drug compounds are mixed with custom adhesives in large specialized kettles.

• After blending is complete, the drug/adhesive mix is pumped to the next machine for coating.

2. Coating process



In the coating process, a thin, precise drug/adhesive layer is applied within tolerances of about one-tenth the thickness of a human hair to long, broad sheets of release liner material.

3. The blending solvent is removed in the large arch tunnel oven

4. Lamination of backing

Then the final layer of the three-layer patch – the backing – is laminated. Although initially applied to the release liner, the adhesive matrix permanently bonds to the patch backing. The completed laminate is then rolled for the next production step

5. Rolling of the laminate

The laminate rolls are then sent through punching, pouching and cartoning machines specially configured for each product.

6. Punching

Dosing is controlled in part by patch size, and patches of precisely the proper size are punched from the laminate sheet

7. Pouching and cartooning

EVALUATION OF TDDS

TESTS DONE ON FINAL PRODUCT	TESTS
CHEMICAL TEST	Content Content uniformity Purity Residual solvent
PHYSICAL TEST	**Release testing** USP apparatus 5 (Paddle over disk) USP apparatus 6 (Cylinder) USP apparatus 7 (Reciprocating disk) Franz Diffusion Cell **Test for adhesion** **Peel adhesion** **Tack property** Thumb tack test Rolling ball tack test Quick-stick (peel tack test) Probe tack test **Shear strength**
CUTANEOUS TOXICITY	Contact dermatitis Growth of microorganisms Cytotoxicity

1. Thickness of the patch:

- The thickness of the drug loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

2.Weight uniformity:

- The prepared patches are to be dried at 60°c for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

3. Folding endurance:

- A strip of specific are is to be cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.

4. Percentage Moisture content:

- The prepared films are to be weighed individually and to be kept in a desiccator containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula.

Percentage moisture content = [Initial weight- Final weight/ Final weight] ×100.

5. Percentage Moisture uptake:

- The weighed films are to be kept in a desiccator at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the films are to be reweighed and determine the percentage moisture uptake from the below mentioned formula.

Percentage moisture uptake = Final weight- Initial weight

6.Water vapour permeability (WVP) evaluation:

- Water vapour permeability can be determined with foam dressing method the air forced oven is replaced by a natural air circulation oven. The WVP can be determined by the following formula

WVP=W/A

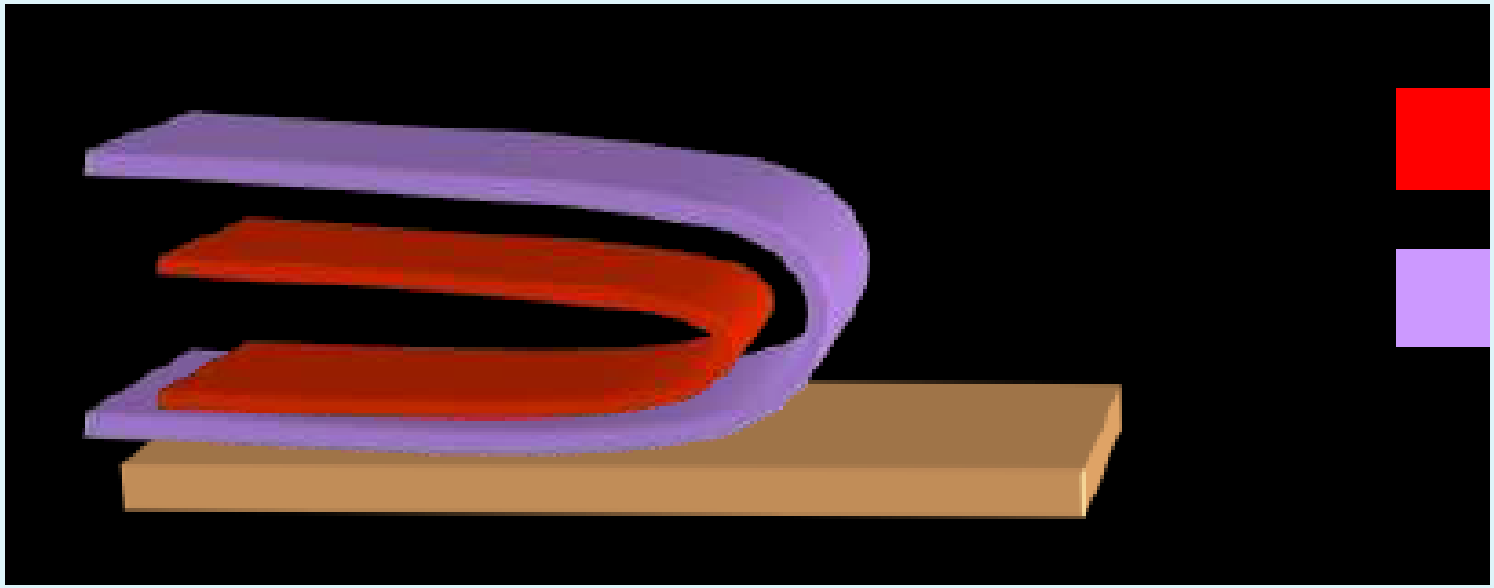
- Where,WVP is expressed in gm/m2 per 24hrs,
- W is the amount of vapour permeated through the patch expressed in gm/24hrs and A is the surface area of the exposure samples expressed in m2.

7. Drug content:

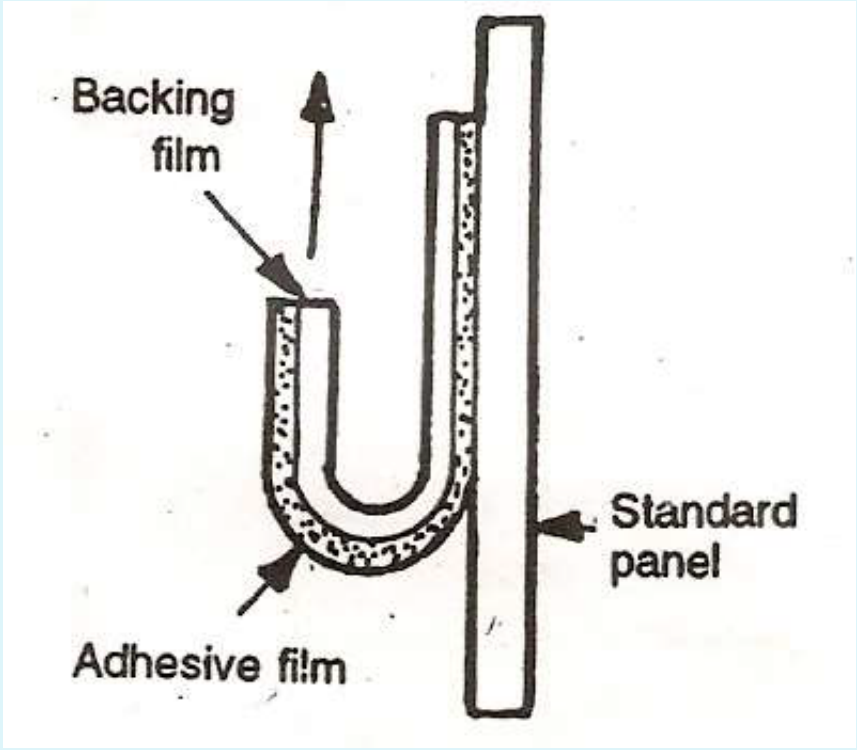
- A specified area of patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyse the drug contain with the suitable method (UV or HPLC technique). Each value represents average of three different samples.

ADHESION TEST

1 PEEL ADHESION TEST



- The force required to remove an adhesive coating from a test substrate is referred to as peel adhesion.
- The force is expressed in ounces (or grams) per inch width of tape.
- If higher value then it indicates greater bond strength.


Backing
film
Standard
panel
Adhesive film

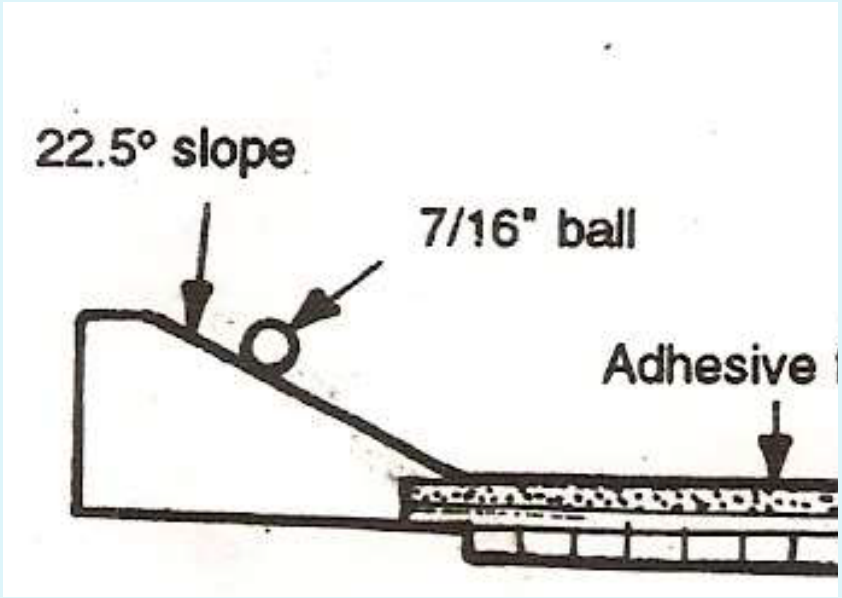

180° Peel Adhesion
STOP

2. TACK PROPERTY :

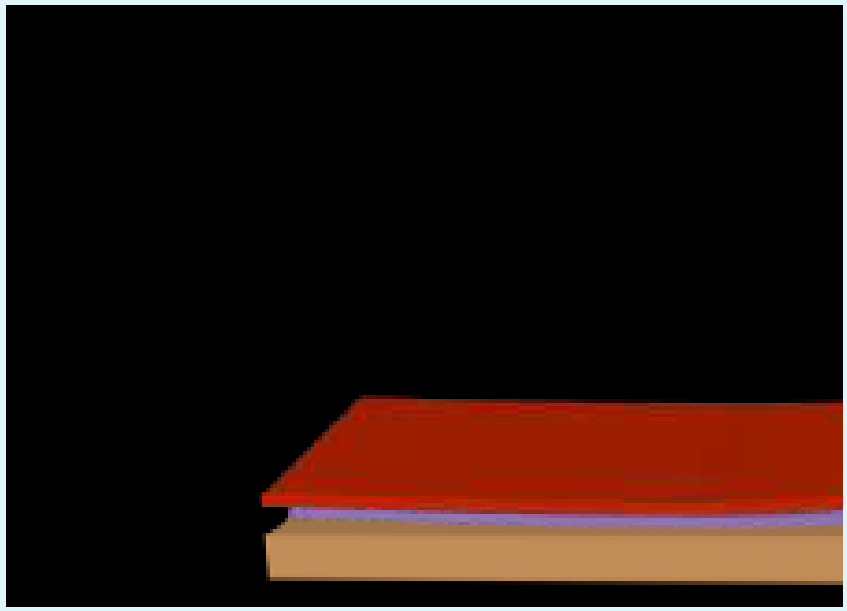
2(a) THUMB TACK TEST

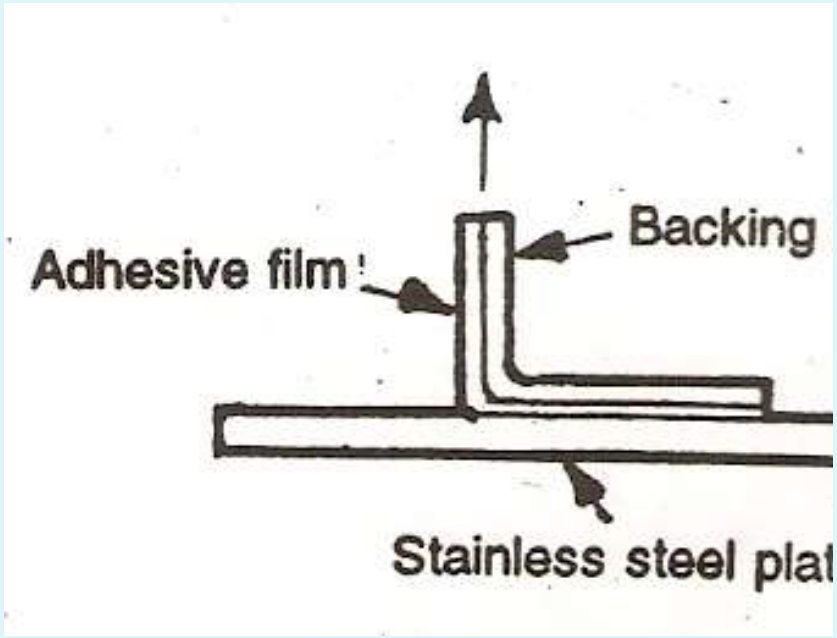
- Qualitative test.
- The thumb is simply pressed on the adhesive and relative tack property is detected

2(b) ROLLING BALL TACK TEST



2(c) QUICK-STICK (PEEL TEST) TEST

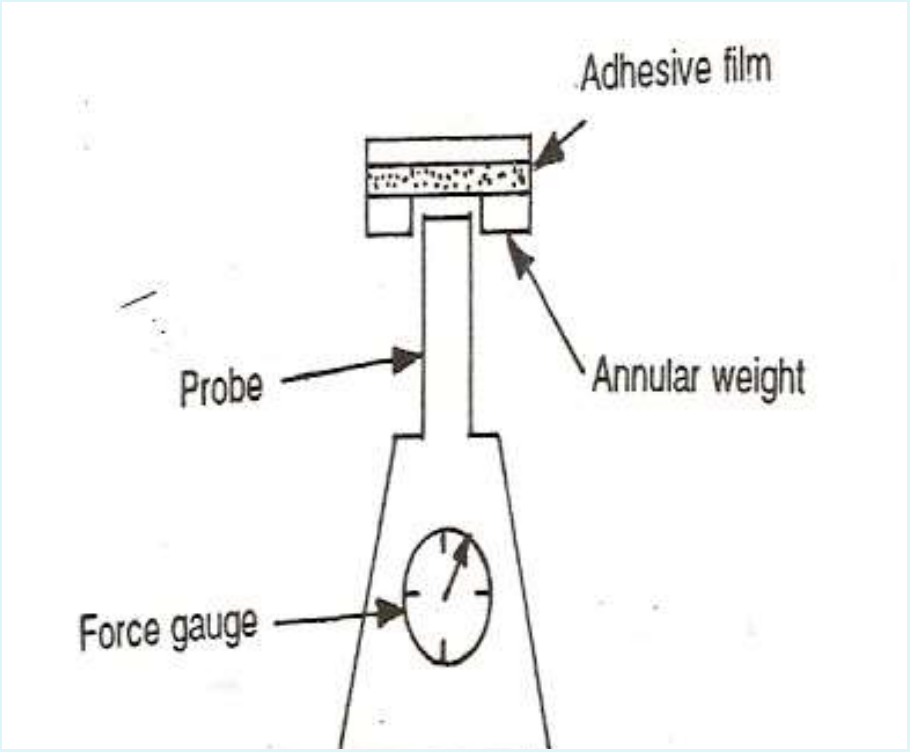




2(d) PROBE TACK TEST

Polyken probe tester

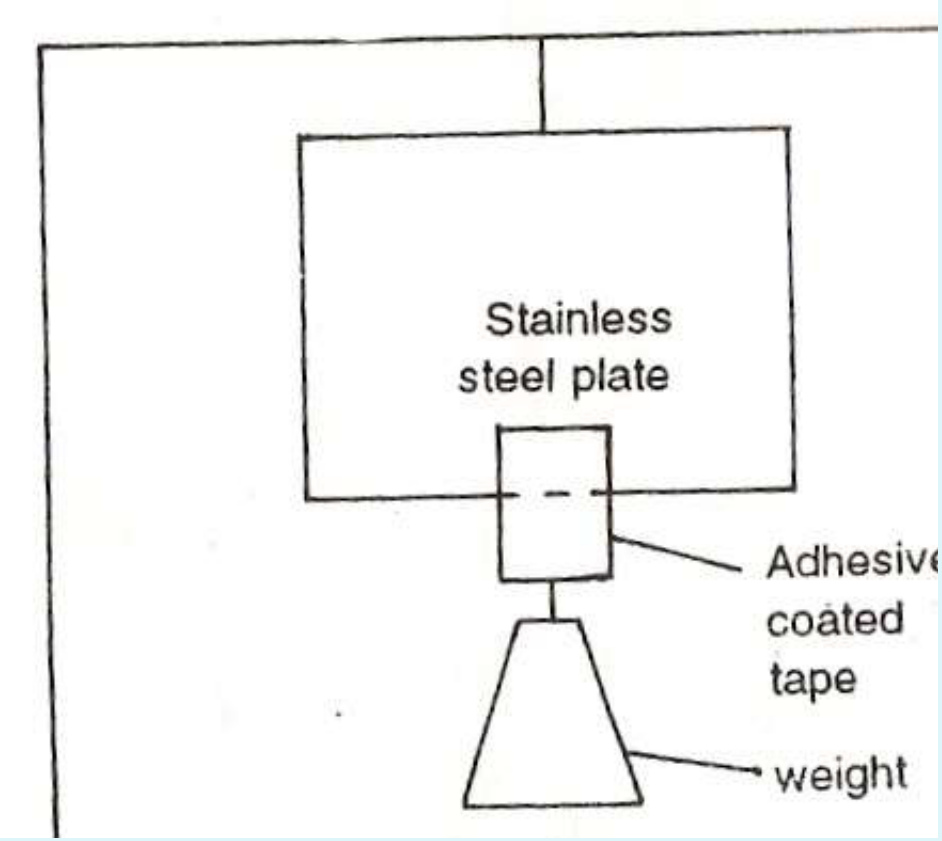
- The tip of clean probe is brought into contact with adhesive, and when a bond is formed between probe and adhesive. The force required to pull the probe away from the adhesive at fixed rate is recorded as tack (Grams).



Shear strength :

- Shear strength is the measurement of the cohesive strength of an adhesive polymer.
- If transdermal device has adequate cohesive strength, it will not slip after application and will leave no residue upon removal. In this particular test, adhesive coated tape is applied onto a stainless steel plate.
- A specified weight is hung from the tape to affect its pulling in a direction parallel to the plate. Shear strength is determined by measuring the time it takes to pull the tape off the plate.
- The longer the time taken for removal, greater is

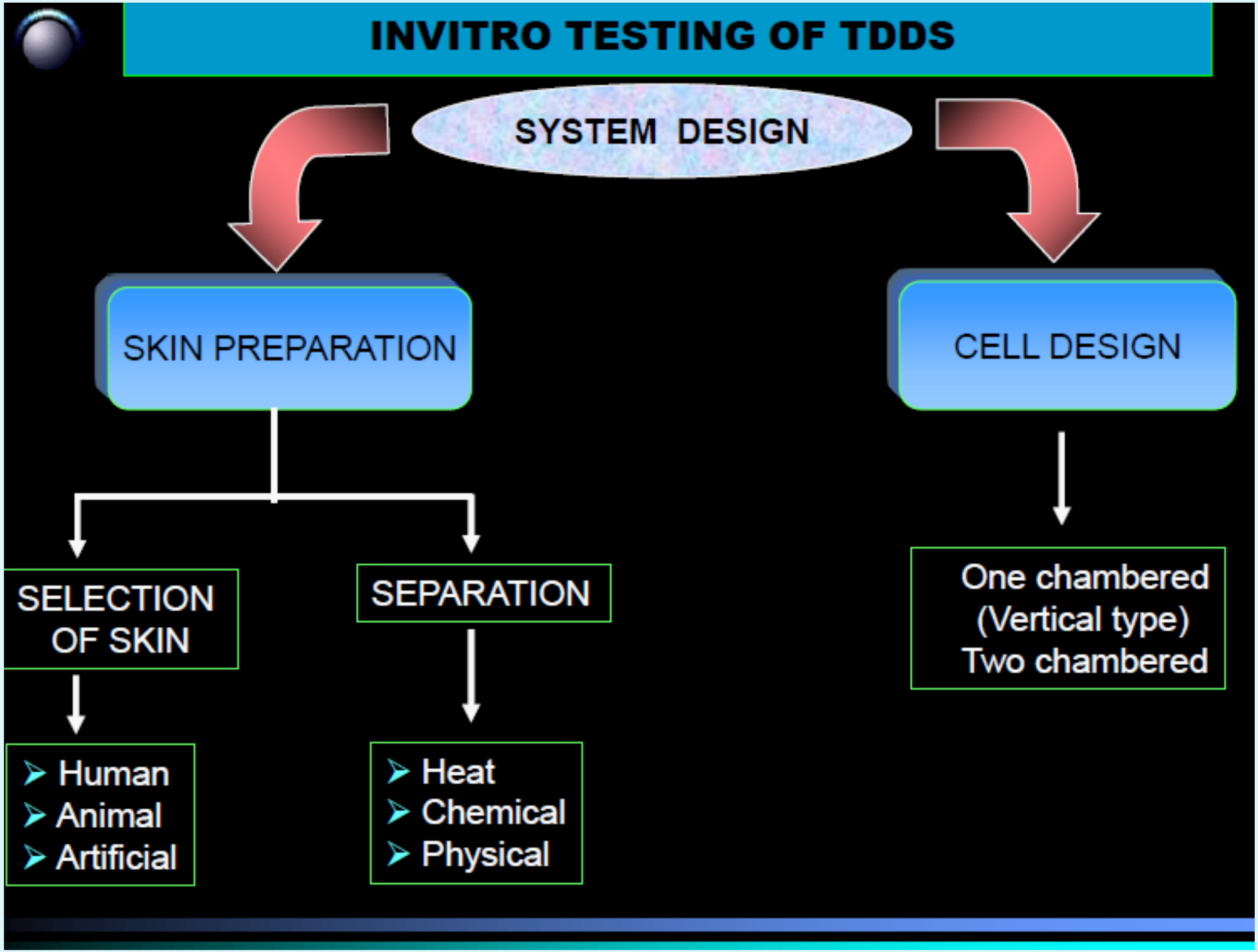
Shear strength properties



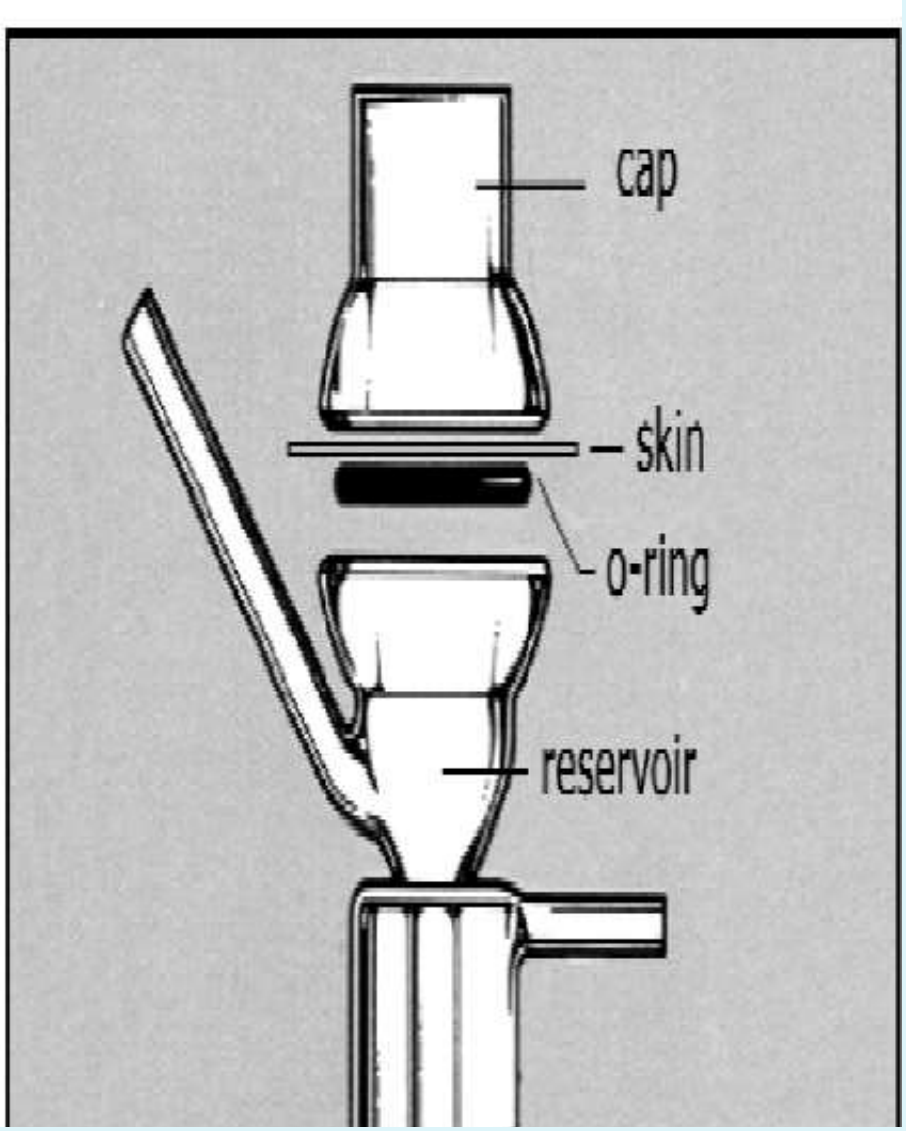
Tensile strength

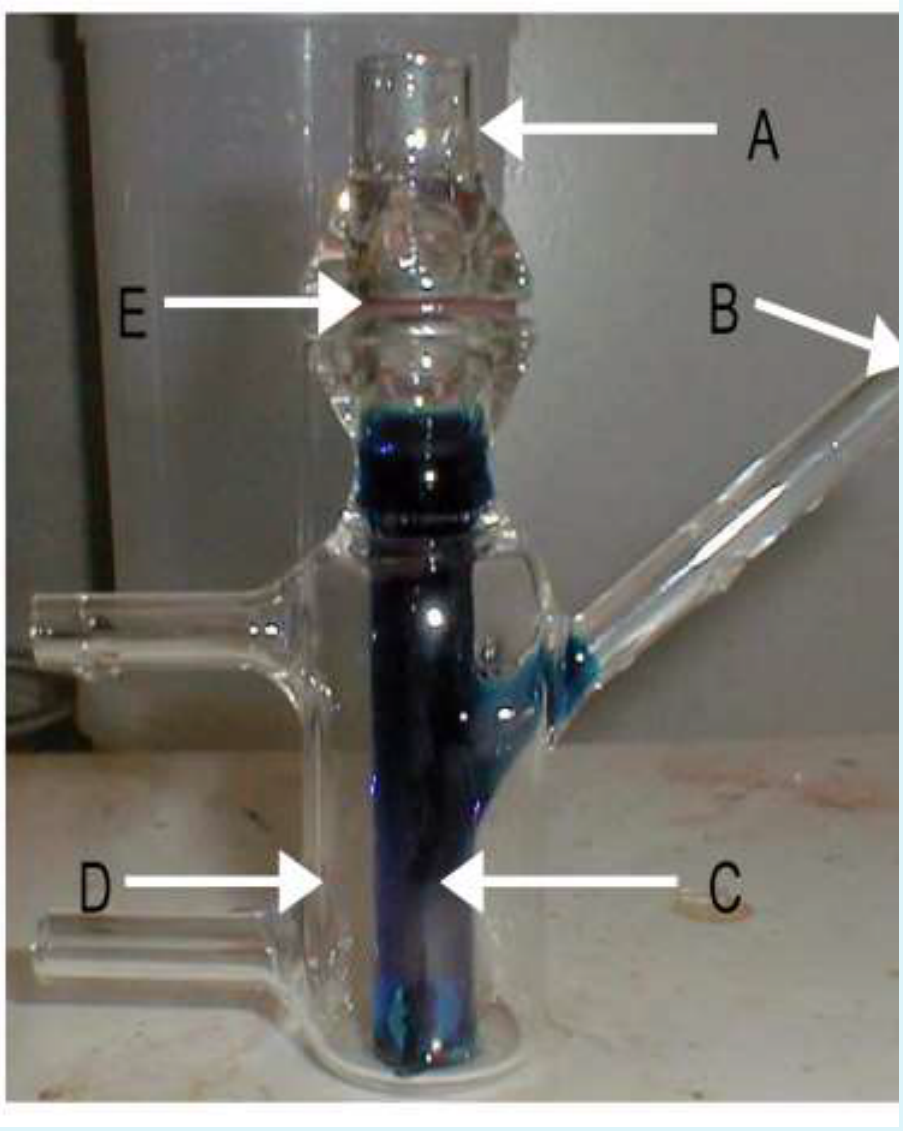
$$\text{Tensile strength} = F/a.b\,(1+L/l)$$

F - the force required to break
a - width of film
b - thickness of film
L - length of film
l - elongation of film at break point


INVITRO TESTING OF TDDS
SYSTEM DESIGN
SKIN PREPARATION
CELL DESIGN
SELECTION OF SKIN
SEPARATION
One chambered
(Vertical type)
Two chambered
Human
Animal
Artificial
Heat
Chemical
Physical

DESIGN OF FRANZ DIFFUSION CELL





- This has a effective permeation area of **1 cm2 and** receptor cell volume of **10ml.**
- A **bar magnet is used for stirring solution in receptor** compartment.

Procedure: (Franz-diffusion cell)

1. The receptor compartment is filled with 10 ml of PBS, stirred at 100 rpm and temp. of 32 ± 1oC is maintained.
2. The skin is carefully checked through magnifying glass to ensure any holes, surface irregularity.
3. The skin is mounted on receptor compartment with stratum corneum side facing up in to the donor compartment.
4. The transdermal system is applied on the skin.
5. samples are withdrawn at regular time intervals through sampling port for 24 hrs and analyzed.
6. The receptor phase is immediately replenished with equal volumes of fresh diffusion buffer.

In-vitro testing

Importance

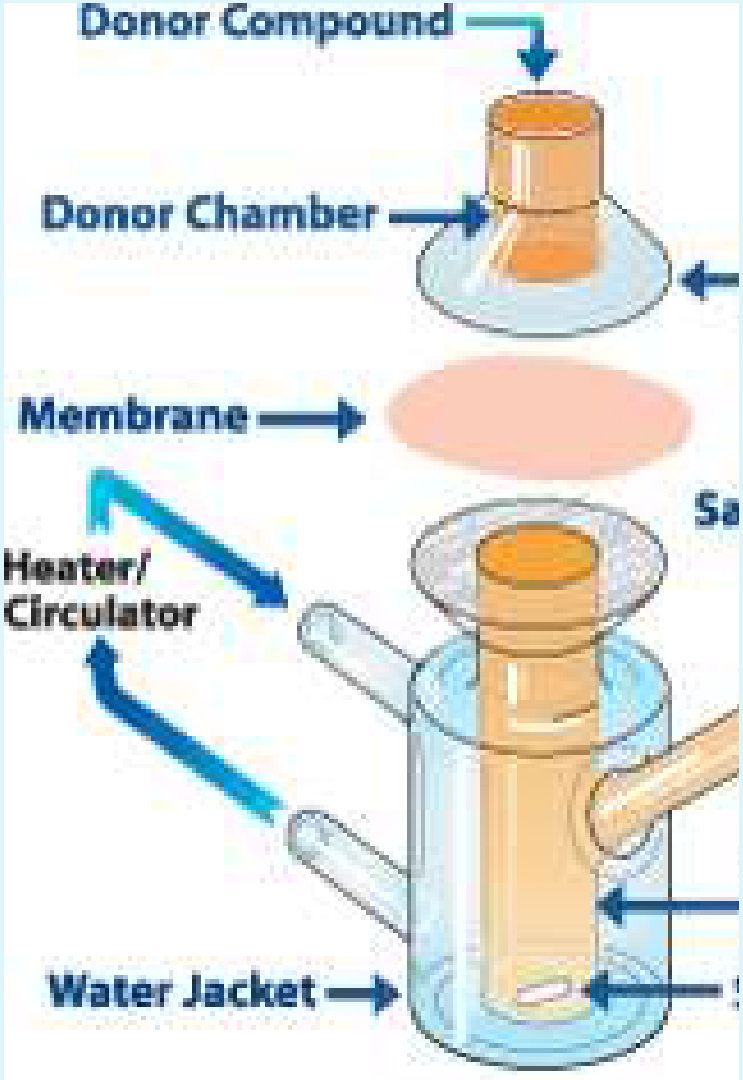
(1)Defining skin permeation kinetic studies using a diffusion cell system and cadaver skin during the drug development process.

(2) *In vitro drug release kinetics, to be used for batch-to batch* release and as a compendial test.

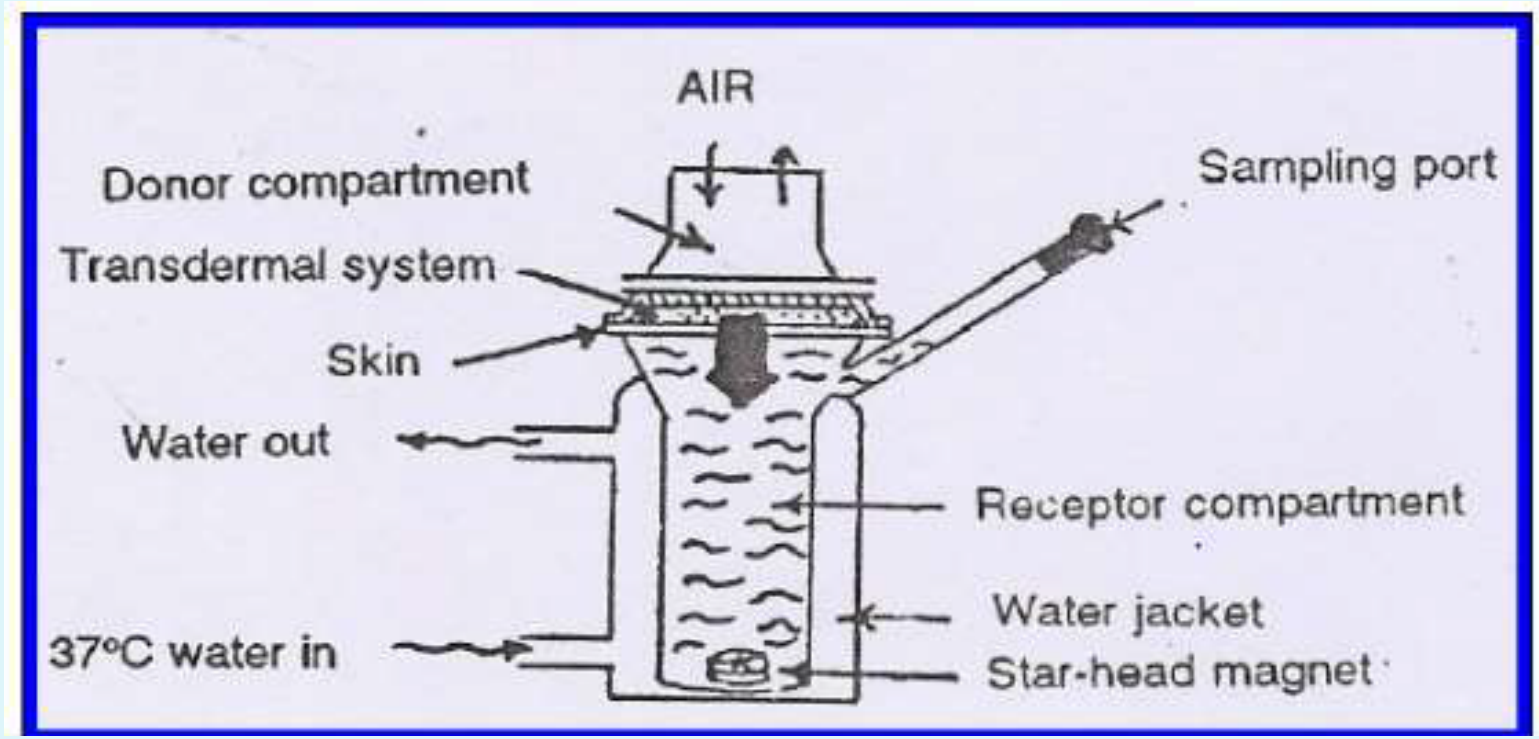
Preparation of skin for permeation studies

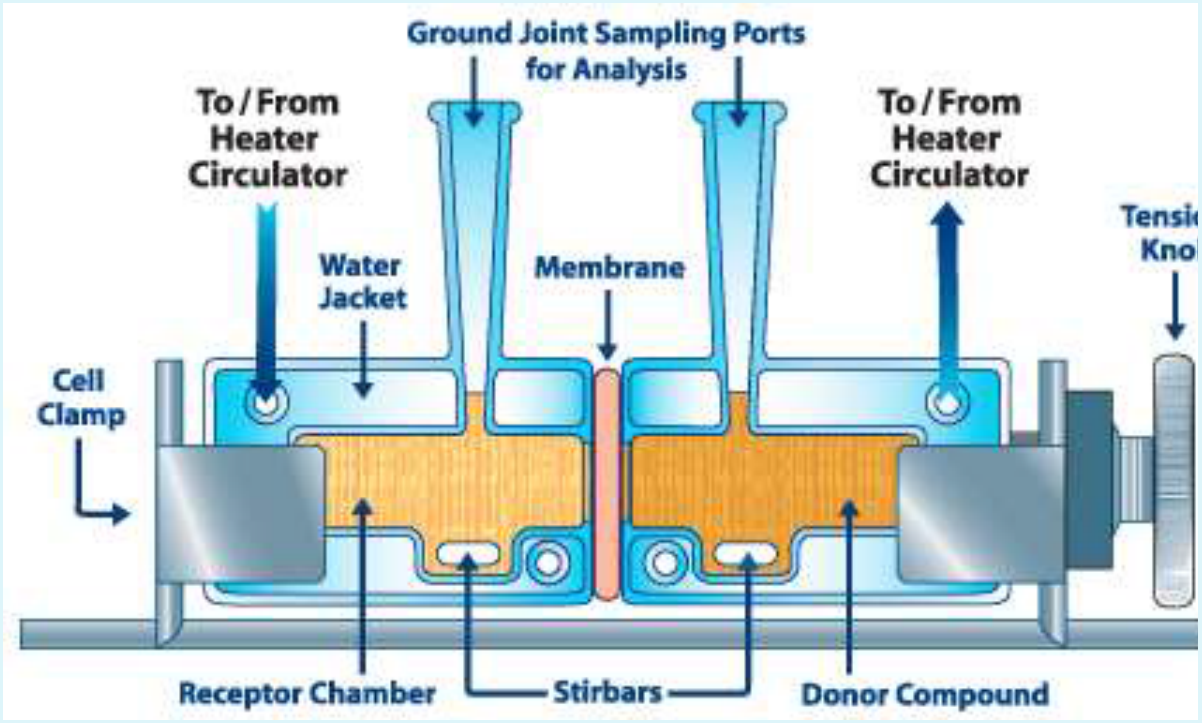
- Intact Full thickness skin
- Separation of epidermis from full thickness skin

K-C(Keshary-Chien) cell for permeation studies



- It has an effective receptor volume **12 ml & a skin** surface area of **3.14 cm2.**
- The receptor solution is stirred by a **star-head magnet** rotating at a constant speed of 600 rpm driven by 3 W synchronous motor.




Ground Joint Sampling Ports
for Analysis
To / From
Heater
Circulator
To / From
Heater
Circulator
Water
Jacket
Membrane
Cell
Clamp
Receptor Chamber
Stirbars
Donor Compound


3.4 ml
3.4 ml

In-vivo assessment

1) Animal model

Mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, Guinea pig

2) Human model

- Phase I clinical trials are conducted to determine mainly safety in volunteers.
- Phase II clinical trials determine short term safety and mainly effectiveness in patients.
- Phase III trials indicate the safety and effectiveness in large number of patient population.
- Phase IV trials at post marketing surveillance are done for marketed patches to detect adverse drug reactions.

Skin irritation studies

Contact dermatitis

- Group I was served as normal, without any treatment.
- Group II, control, was applied with marketed adhesive tape.
- Group III Transdermal systems (blank)
- Group IV Transdermal systems (drug loaded)
- Group V standard irritant .
- Skin irritancy studies (Erythema) ---- Modified draize test.

Skin uptake and Metabolism:

- Skin possess ability to metabolise drug hence research can be focused on prodrug approach.

  Procedure:

  1. A skin piece of (3x3 cm) is mounted between 2 compartments of Valia- Chien (V-C) cell maintained at 37°C.
  2. The stratum corneum is exposed to drug saturated solution of drug in normal saline and other side of the skin is protected with impermeable aluminum foil.
  3. Samples are withdrawn at regular time intervals and analyzed for metabolites.

Evaluation of skin reactions.

Skin reaction	Sc
A) Erythema and Eschar formation:	
Very slight erythema	
Well defined erythema	
Moderate to severe erythema	
Severe erythema	
Total possible erythema score	
B) Edema formation	
Very slight edema	
Slight edema	
Moderate edema	
Severe edema	
Total possible edema score	
Total possible score for primary irritation	

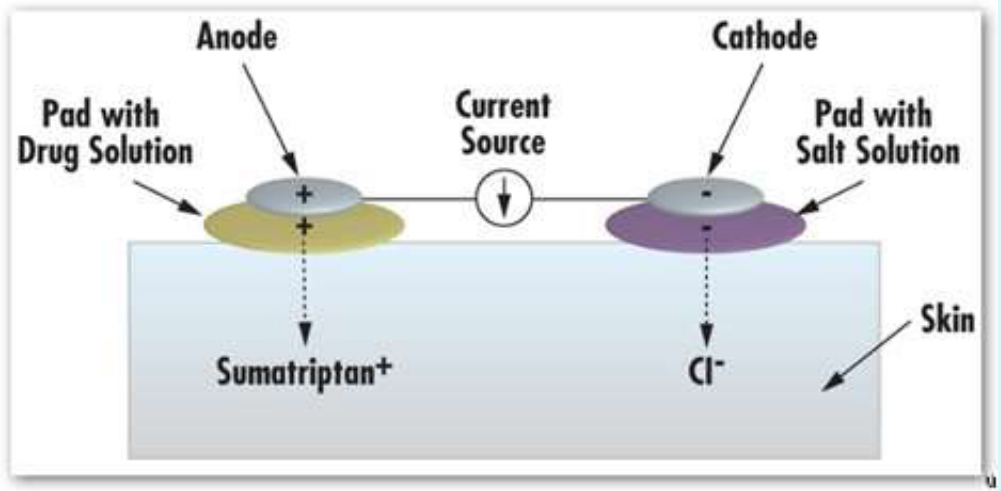
Stability studies

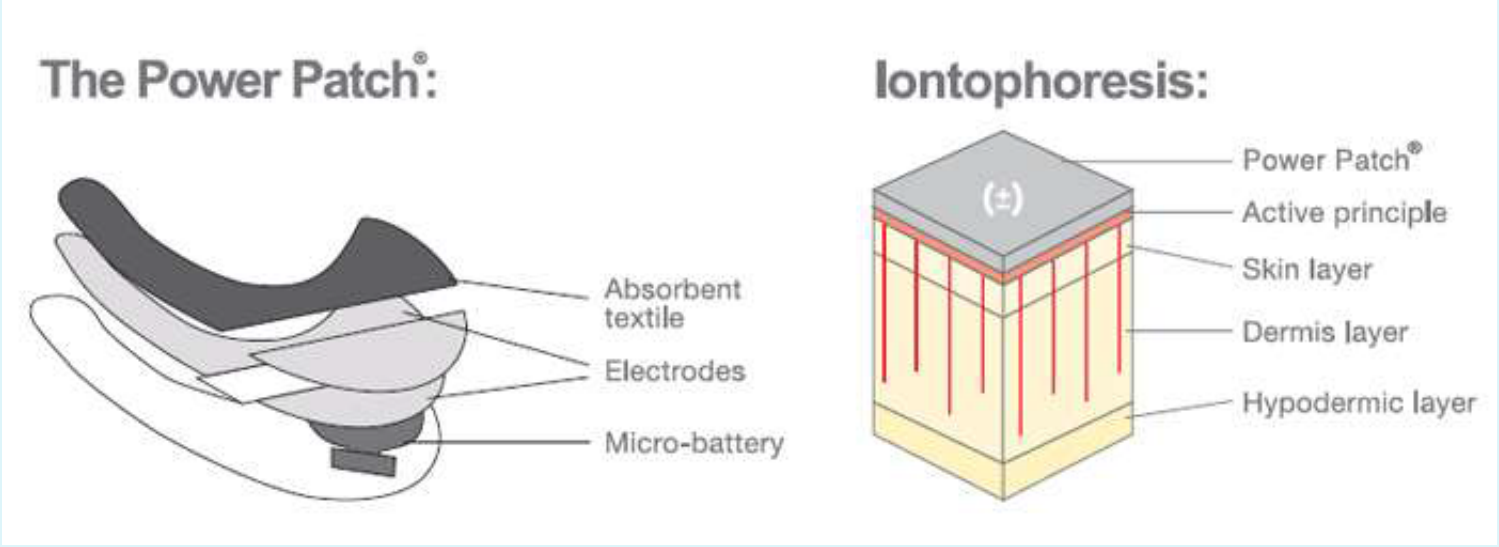
Study	Storage conditions		Time
	Temperature	Relative humidity	
Long Term	25°C± 2°C OR 30°C± 2°C	60%± 5% OR 65%± 5%	12 m
Intermediate	30°C± 2°C	65%± 5%	6 m
Accelerated	40°C± 2°C	75%± 5%	6 m

Novel products

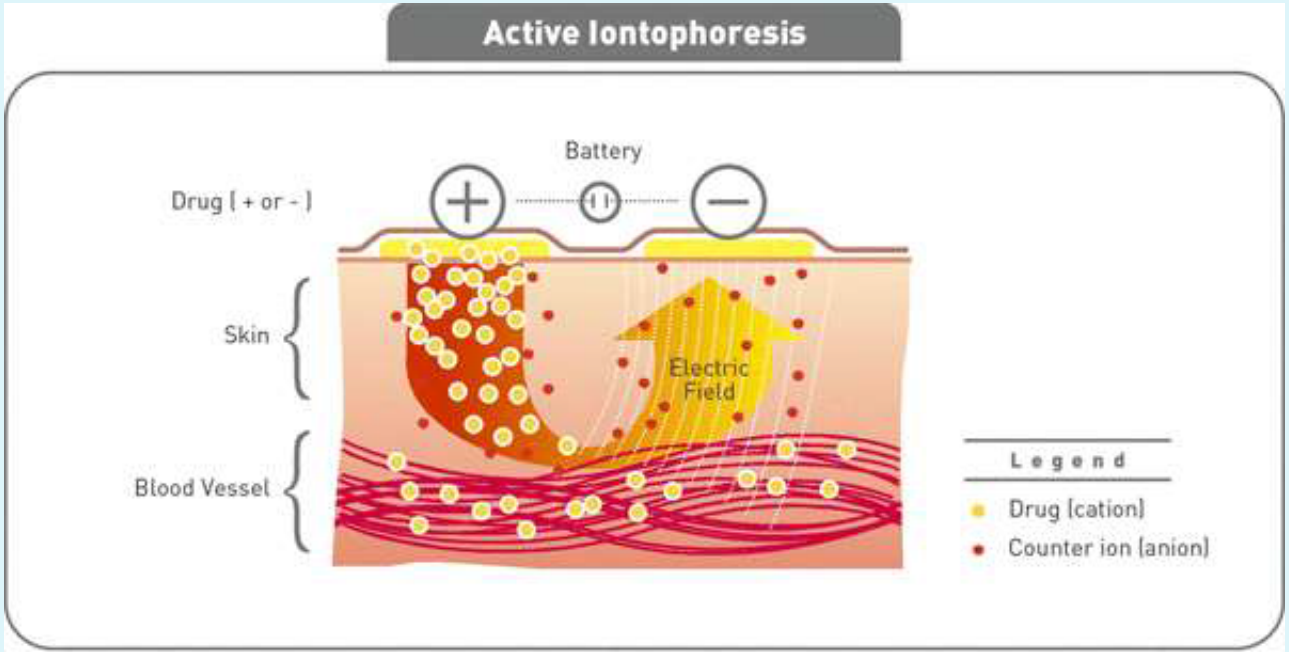
Iontophoretic Patches

- Iontophoretic patches use a tiny electrical current to promote flow of the drug (usually charged) through the skin.





Iontophoretic Patches



LidoSite®

The first FDA-approved pre-filled active anesthetic patch

LidoSite® (Lidocaine HCl/Epinephrine Topical Iontophoretic Patch) 10%/0.1% — Vyteris' revolutionary active patch — provides fast, effective analgesia prior to blood draws, venipunctures, and other superficial dermatological procedures.[1,2] A quick, noninvasive ten-minute application delivers lidocaine, a trusted anesthetic, deep into the skin, significantly reducing the pain of needles.[1,2]

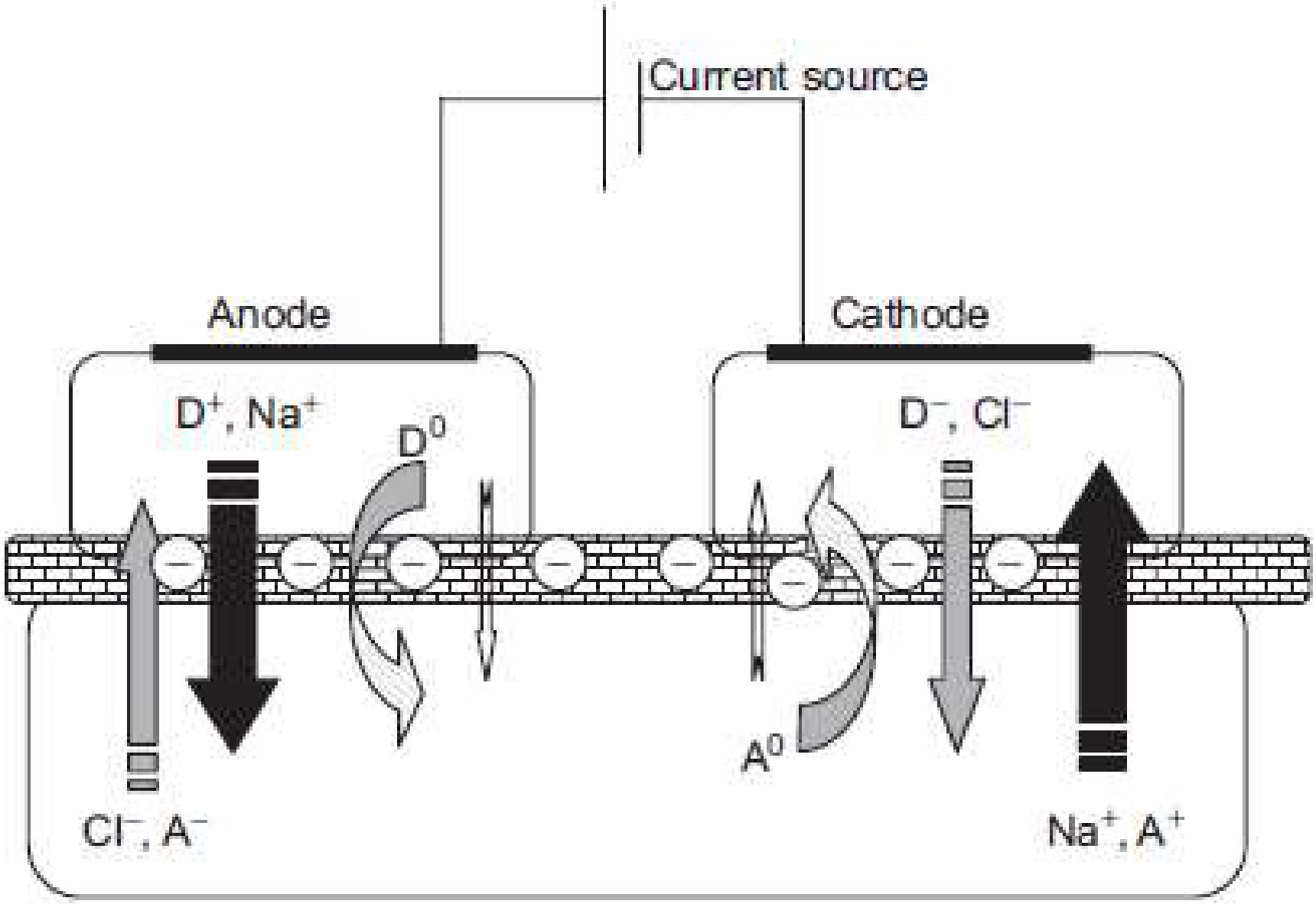
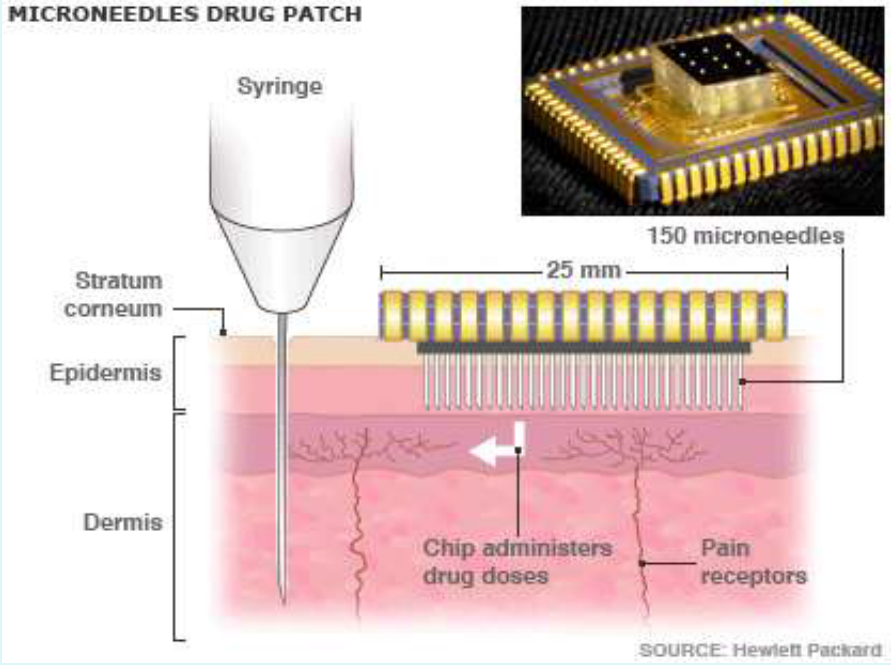


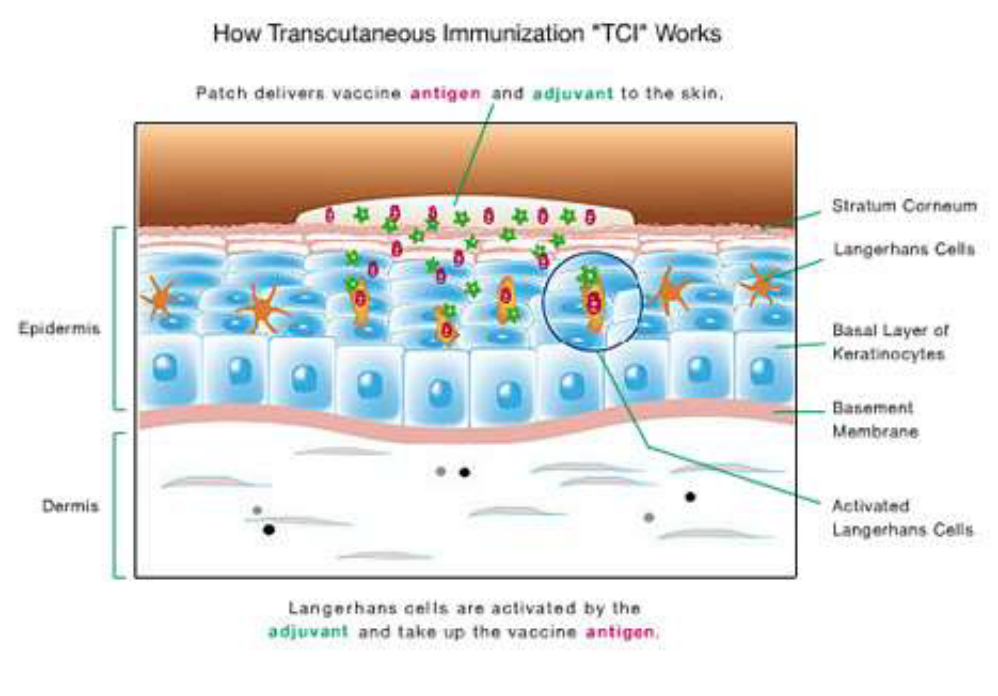
Figure 1. Transport mechanisms of iontophoresis. Letters repre-

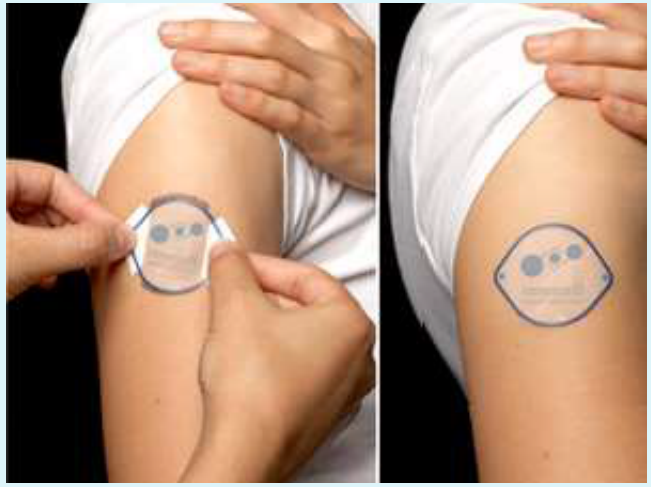
Microneedles Patches

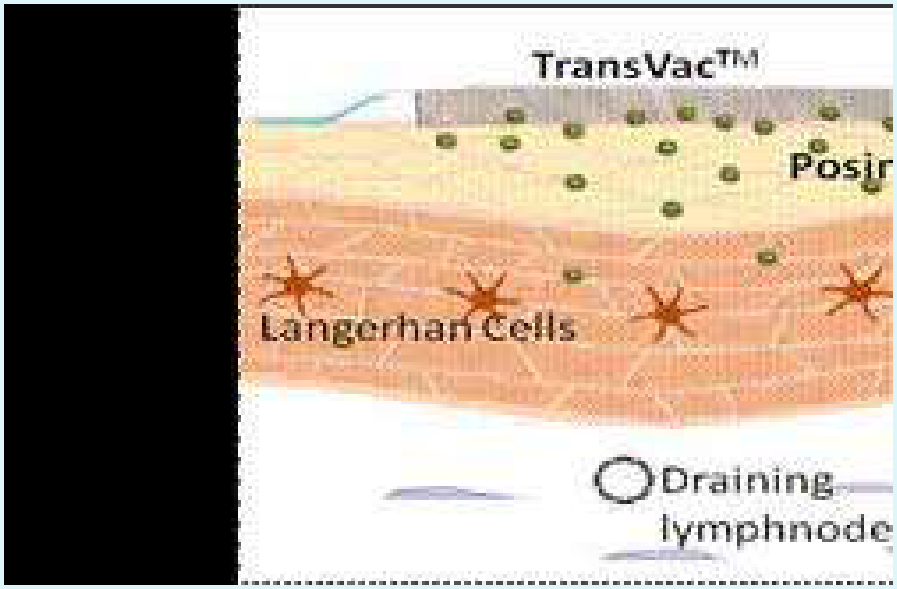


Microneedles patches are currently being explored as mechanisms to deliver vaccines and larger macromolecules.

Transdermal Vaccine Technology







- The microneedle technology can result in more effective contact of the vaccine with the antigen-presenting Langerhans cells
- The needles can be fabricated to be long enough to penetrate the stratum corneum, but short enough to not come into contact with nerve endings.

Table 1 Transdermal Controlled-Release Products and Devices

Drug	Trade Name	Type of Devices	Indication
Scopolamine	Transderm-Scop	Reservoir	Motion sickness
Nitroglycerine	Transderm-Nitro	Reservoir	Angina
	Nitro-Dur	Monolithic	
	Nitrodisc	Monolithic	
Estradiol	Estraderm	Reservoir and ethanol enhancer	Hormone treatment

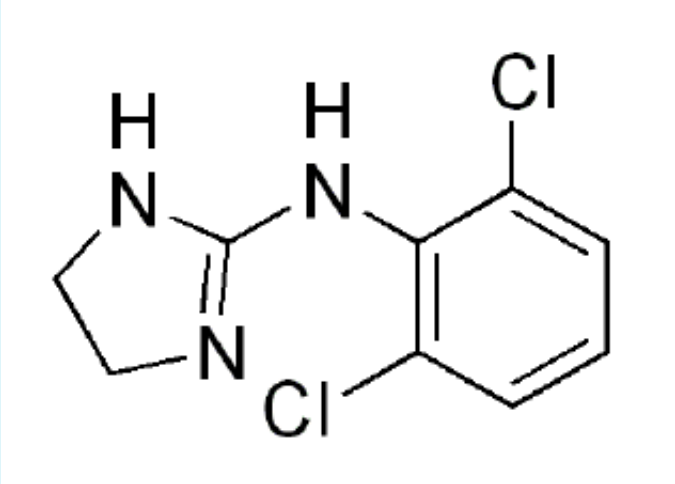
Table 2 transdermal products under development

Drug	Trade name	Producer-Marketer
Minocycline	Sunstar	American Cyanamide, Takeda
Estradiol+Norethisterone	Estracombi TIS	Ciba-Geigy, Alza
DHEA		Pharmedic
Fentanyl		
Triamcinolone acetonide		Whitby Pharm.

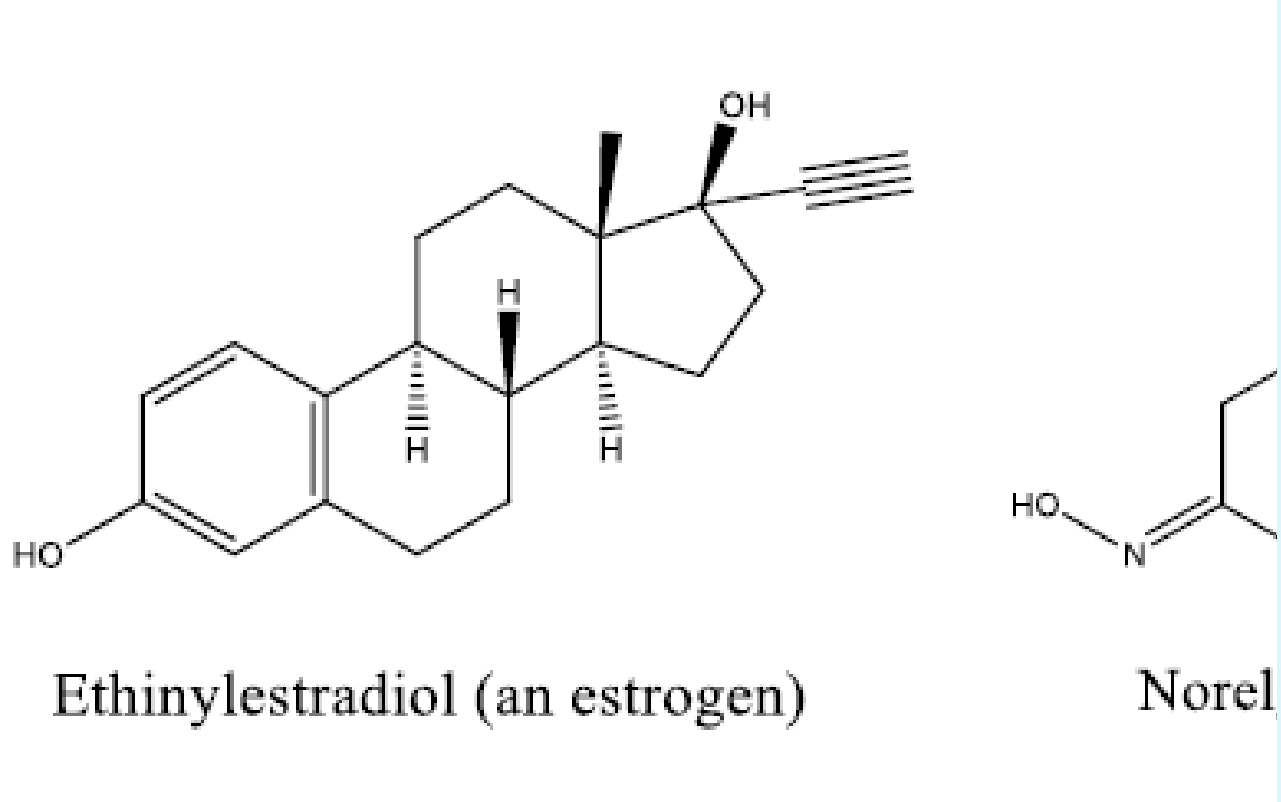
Manufacturer	Trade name	Drug	Strength av
Ciba	Estraderm	Estradiol	25 µg, 50 µg
	Transderm-Scop	Scopolamine	1.5 m
	Transderm-Nitro	Nitroglycerin	0.1 mg, 0.
Janssen	Duragesic	Fentanyl	25 µg, 50 µg
Basel	Habritol	Nicotine	21 µg
Parke-Davis	Nicotrol	Nicotine	21 µg
Lederle	Prostep	Nicotine	21 µg

PRODUCTS ON THE MARKET, OR IN DEVELOPMENT INCLUDE:

- Clonidine
- Works as an agonist of adrenaline at the presynaptic a2 adrenergic
- Product name = Catapres-TTS®
- Used to treat hypertension



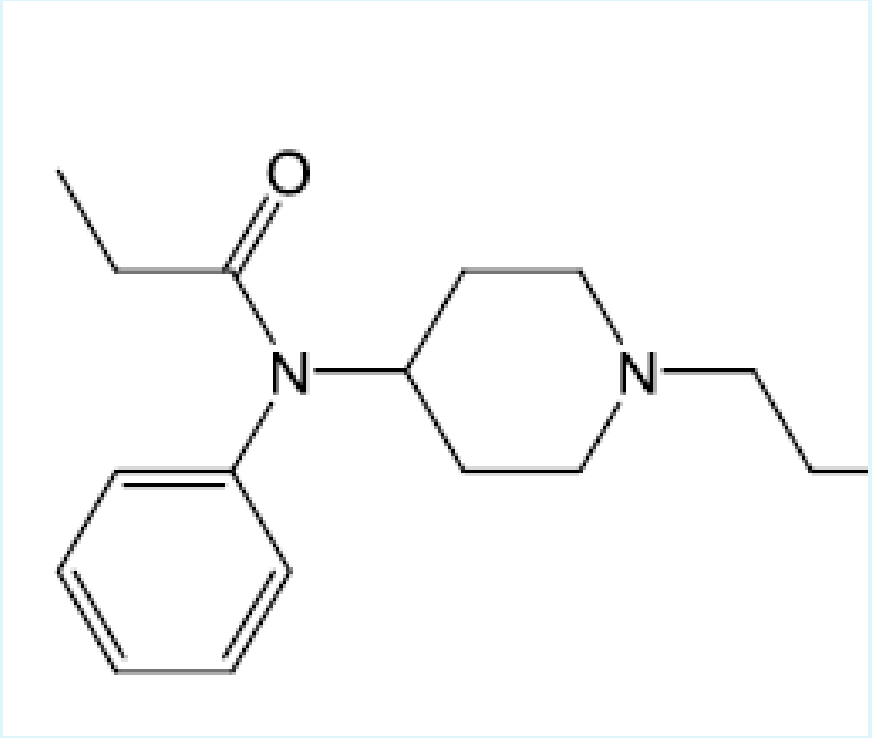
- Ethinylestradiol (EO) and norelgestromin (N)
- Product name = Ortho-Evra®
- Used for Contraception
- Type of patch = Drug-in-Adhesive
- Frequency of application = weekly



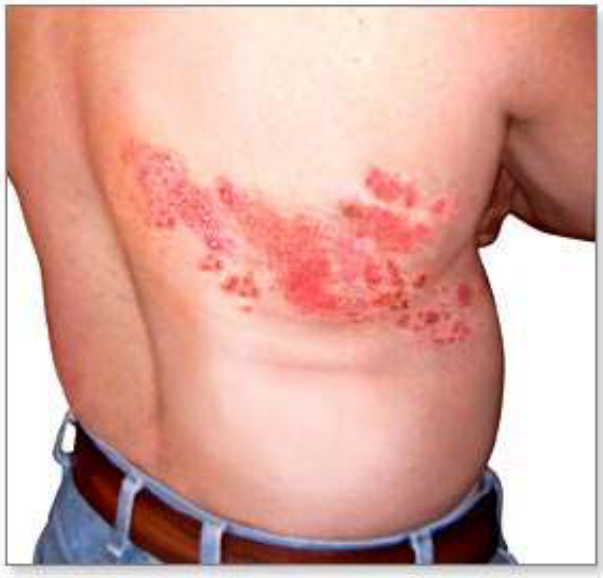
Ethinylestradiol (an estrogen)

Norel

- Fentanyl
- Product Name = Duragesic®
- Used for: Analgesia
- Type of Patch = Drug-in-Adhesive
- Frequency of Application = Weekly

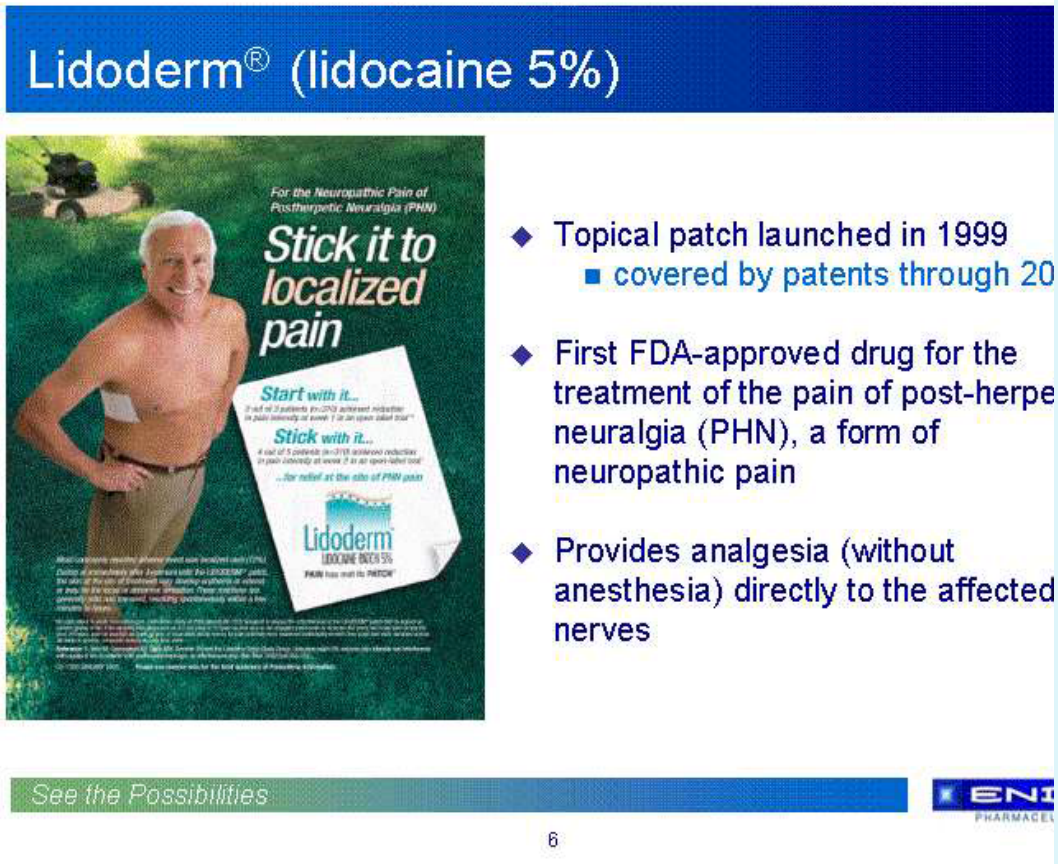


- Lidocaine
- Product Name = Lidoderm®
- Used for: analgesia of postherpetic neuralgia (PHN), a painful condition caused by the varicella zoster virus (herpes zoster = shingles)

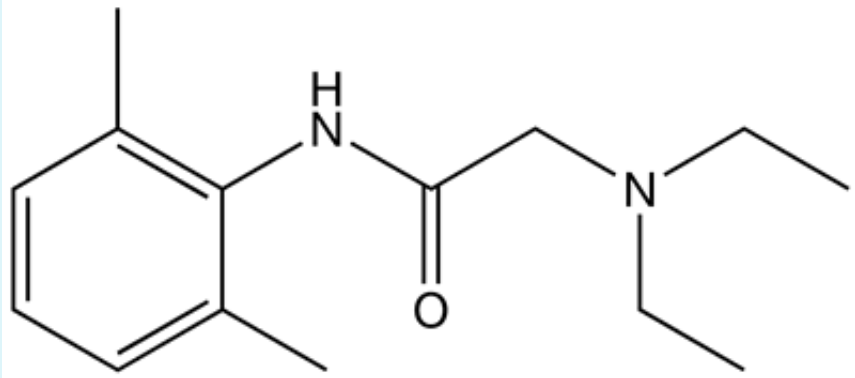


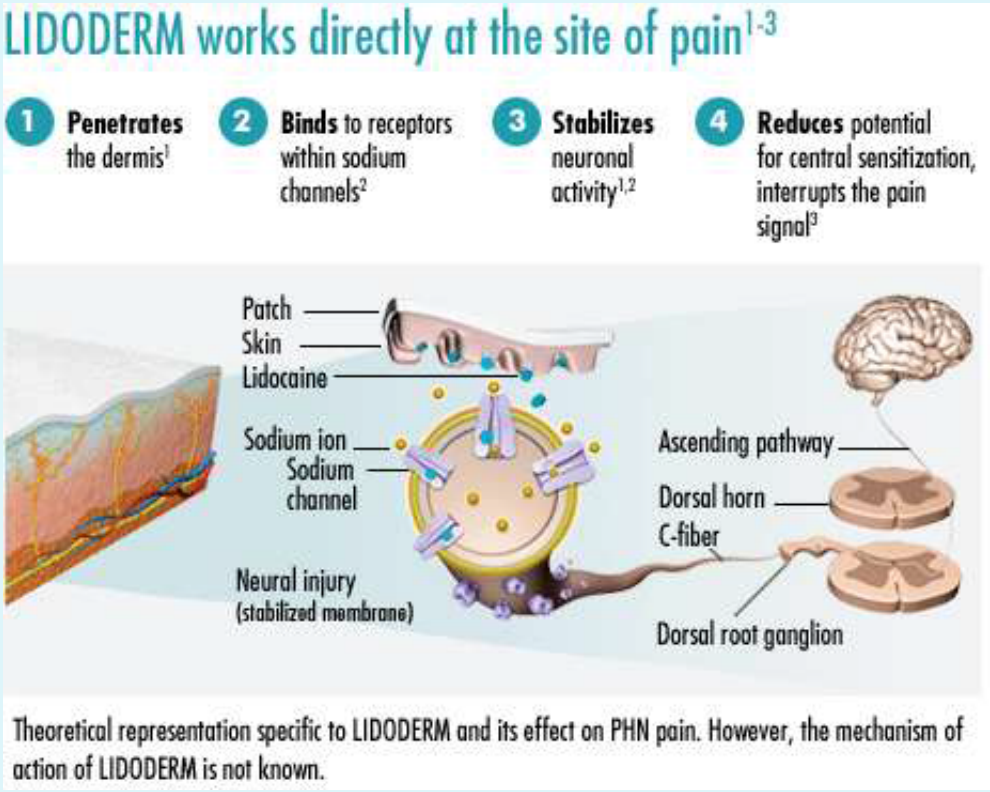
Zoster

A.D.A.M.



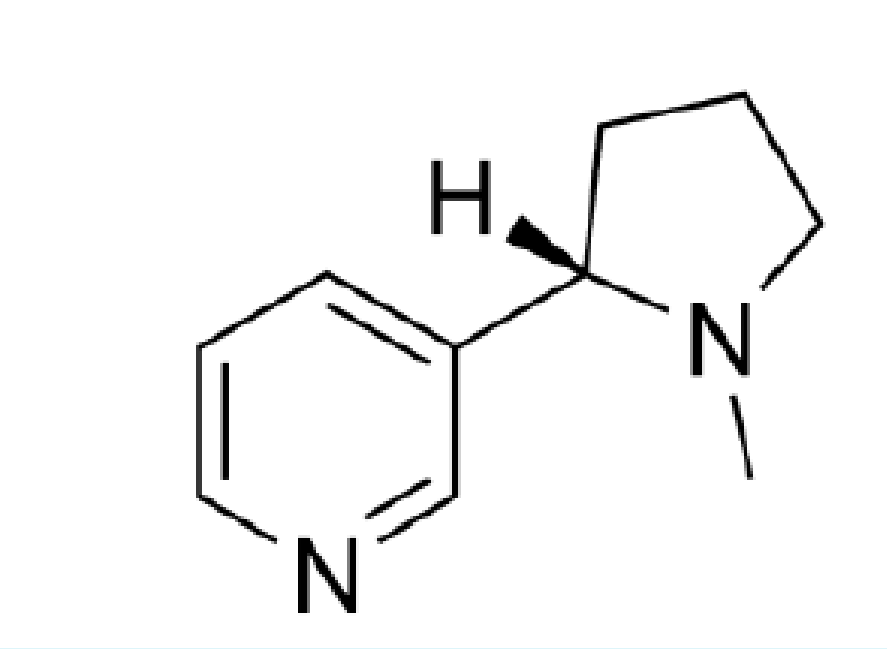
Lidoderm Patch



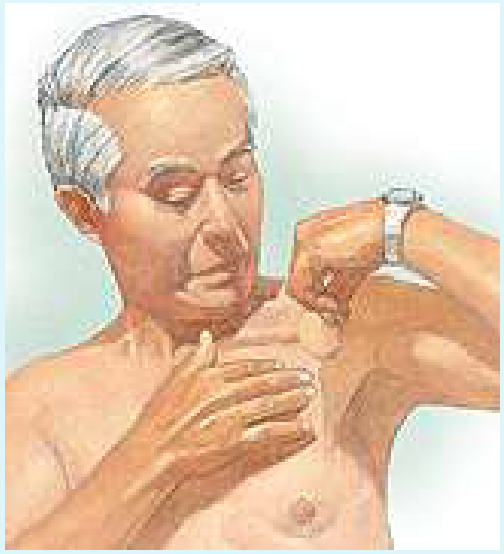


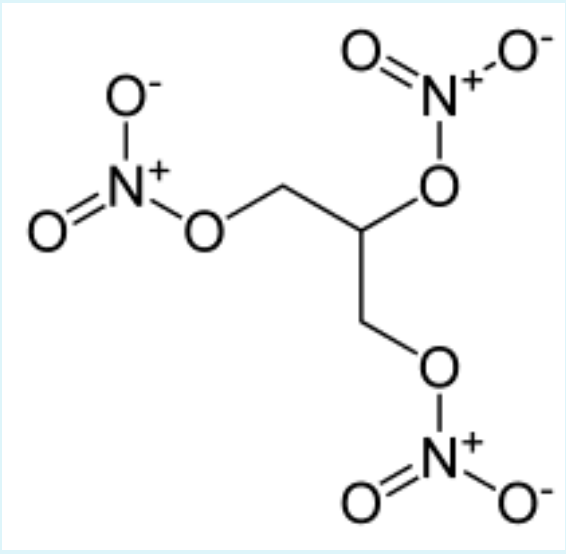
- Type of Patch = Reservoir
- Frequency of Application = Daily

- Nicotine
- Product name = Habitrol®, Nicoderm – CQ®, Nicotrol®, Prostep®
- Used for: Smoking cessation
- Frequency of administration = Daily

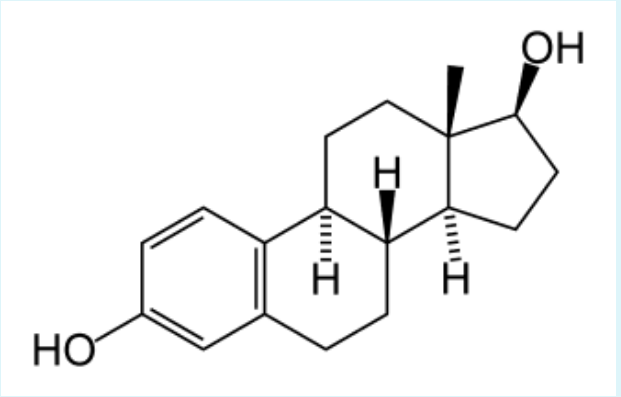


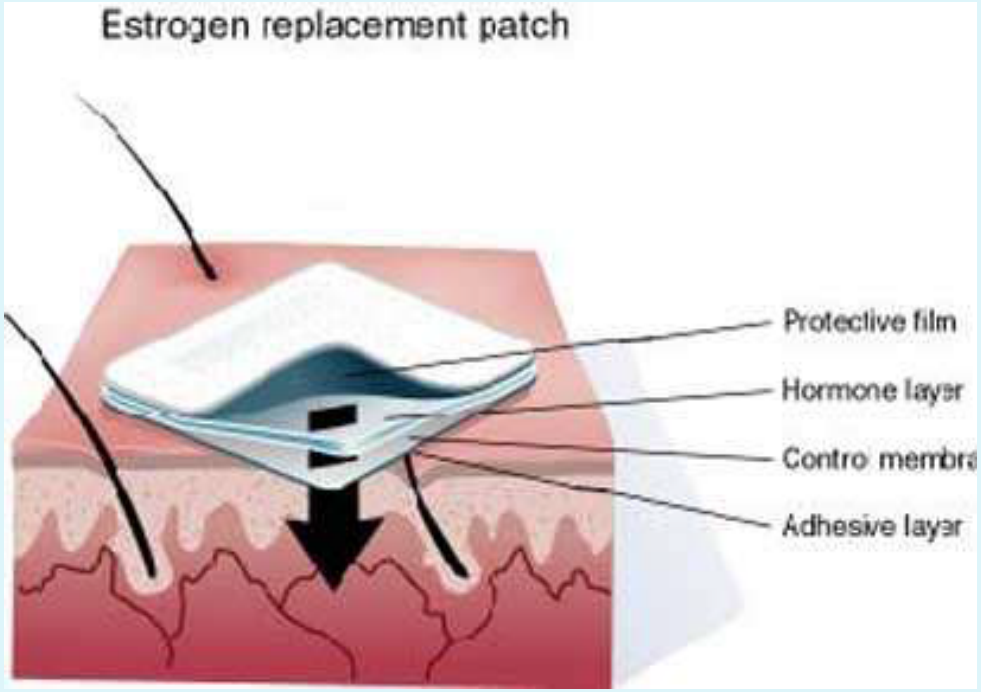
• Nitroglycerin
• Works by producing nitric oxide (NO), which then acts as a vasodilator
• Product Names = Nitro-Dur®, Transderm-Nitro®
• Used for: Angina
• Type of Patch = Nitro-Dur is Drug-in-adhesive Nitrodisc is reservoir
• Frequency of administration = Daily



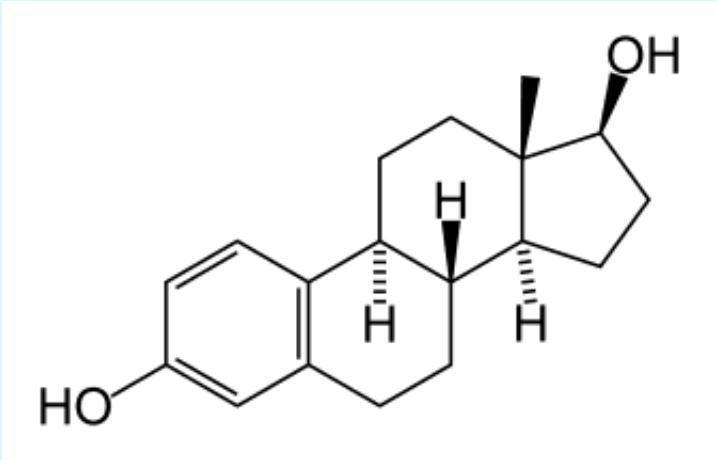


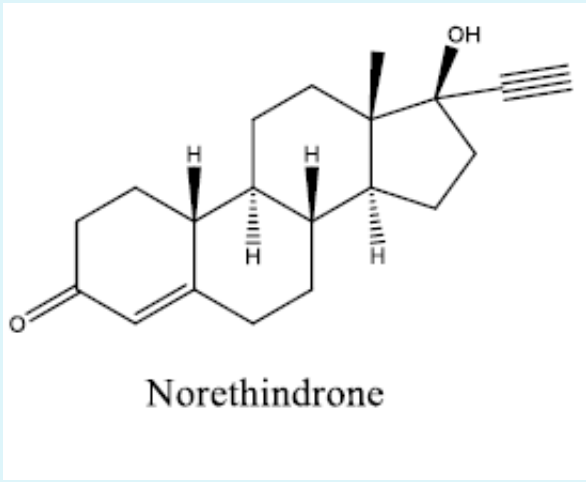
- Estradiol
- Product Name = Alora®, Climara®, Esclim®, Estraderm®, FemPatch®, Vivelle®, Vivelle-DOT®
- Used for: Hormone replacement
- Type of Patch: Drug-in-adhesive
- Frequency of application = weekly





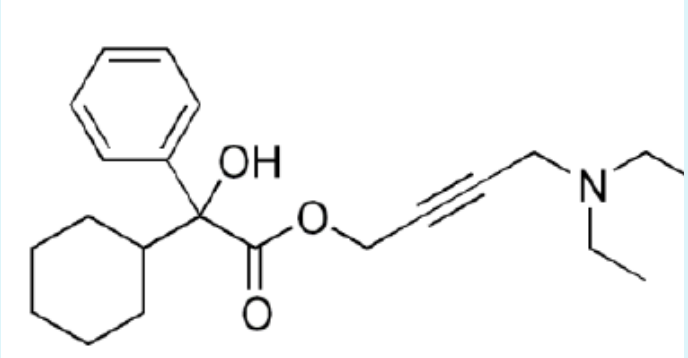
- Estradiol + Norethindrone
- Product name = CombiPatch®
- Used for: Hormone Replacement





Norethindrone

- Oxybutynin
- Works as competitive antagonist of the muscarinic acetycholine receptor
- Product name = Oxytrol®
- Used for: Overactive bladder (antispasmodic)
- Type of Patch: Drug-in-adhesive
- Frequency of application = twice a week



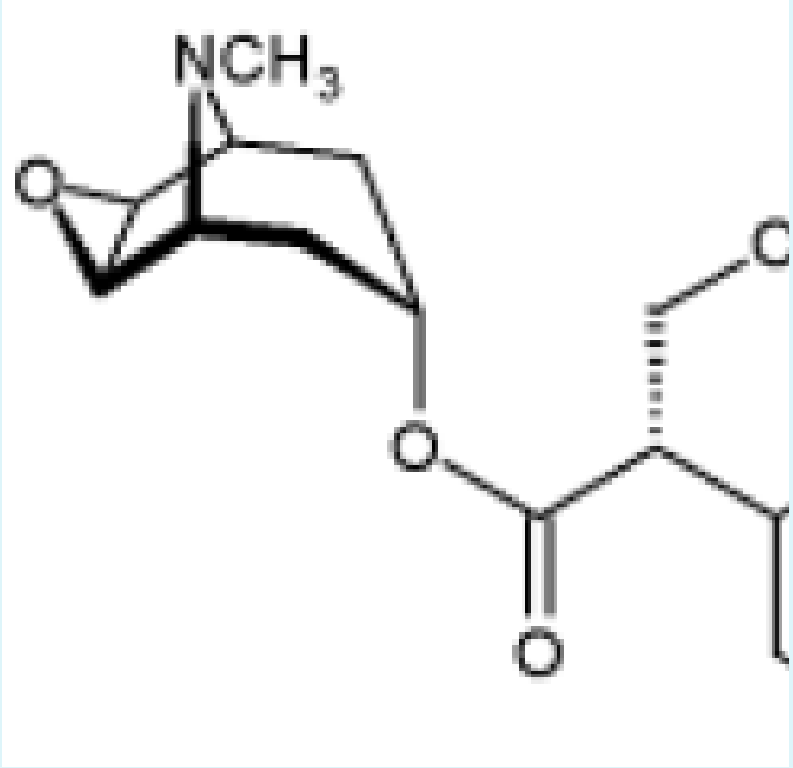
OXYTROL™
Oxybutynin Transdermal System

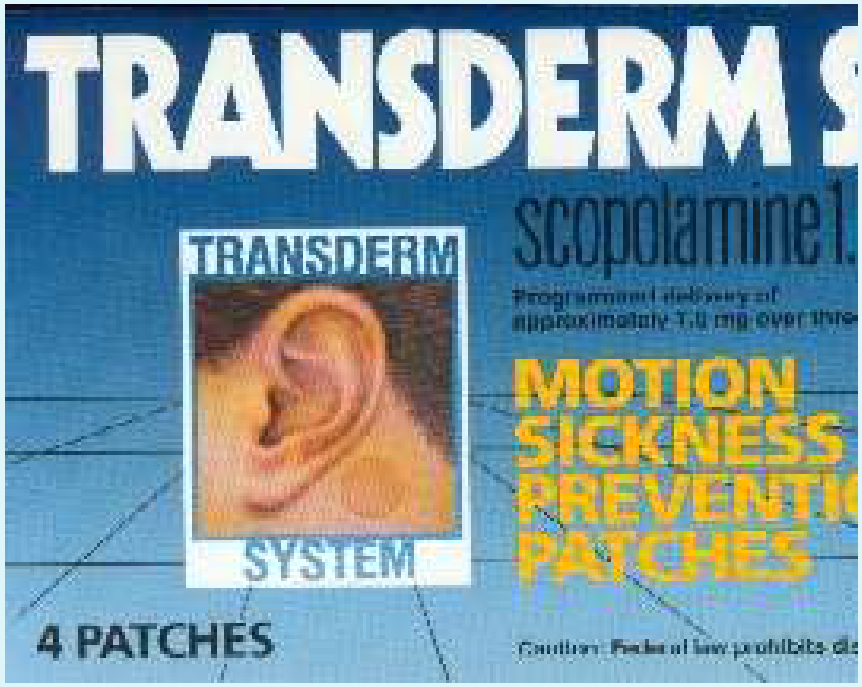
Oxytrol Patch Approved by FDA for Overactive Bladder

CORONA, Calif., Feb 26, 2003---Watson Pharmaceuticals, Inc. announced today that the U.S. Food and Drug Administration has approved Oxytrol (oxybutynin transdermal) for treatment of overactive bladder (OAB). The patch is the first transdermal system for treatment of this condition, which is estimated to affect more than 33 million Americans.

Although the active ingredient (oxybutynin) has been available in pill form for years, side effects---especially dry mouth and constipation---have been a limiting problem for many patients. With the patch, these side effects are less frequent and less severe than with oral forms of the drug. In the clinical trials leading to FDA approval, side effects in the Oxytrol group were about the same as in the placebo group. Thus, transdermal delivery of the drug appears to offer an advantage over the oral

- Scopolamine
- Works as competitive antagonist of acetylcholine at the muscarinic receptor
- Product Name = Transderm Scop®
- Used for: Motion Sickness





- Lidocaine + Epinephrine
- Product name = Lidosite
- Used for: Dermal anesthesia
- Type of Patch = Reservoir, iontophoretic.
- Epinephrine acts as vasoconstrictor, thus prolonging the duration of action of lidocaine (by delaying resorption) at the site