Shree H. N. Shukla Institute of Pharmaceutical Education and Research, Rajkot

B. Pharm
Semester-VII

Subject Name: Novel Drug Delivery System
Subject Code: BP704TT

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CHAPTER-2- Unit:2- TRANSDERMAL DRUG DELIVERY SYSTEM

SYLLABUS:

Transdermal drug delivery system:

Introduction, Permeation through skin, factors affecting permeation, permeation enhancers, basic components of TDDS, formulation approaches

This subject is designed to impart basic knowledge on the area of novel drug delivery systems.

Learning objectives

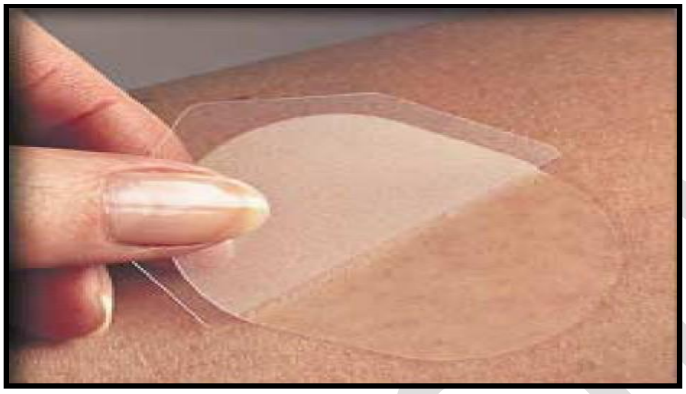
Upon completion of the course the student shall be able to

1. To understand various approaches for development of novel drug delivery systems.
2. To understand the criteria for selection of drugs and polymers for the development of Novel drug delivery systems, their formulation and evaluation.

Transdermal Drug Delivery System

What is Transdermal Drug Delivery System (TDDS)

- Transdermal drug delivery system is formulation that is applied to the body surface and is designed to deliver the active drug across the skin, into the systemic circulation.



- Worldwide market revenues for transdermal products are US$3B,
- Shared between the USA at 56%, Europe at 32% and Japan at 7%.
- 1970-- Alza Research (US) began first development of the modern transdermal
- 1980-- Scopolamine first transdermal reached US
- 2002– Many Rx and non-RX products in US market.
- Transdermals deliver drugs from a few hours up to 7 days.

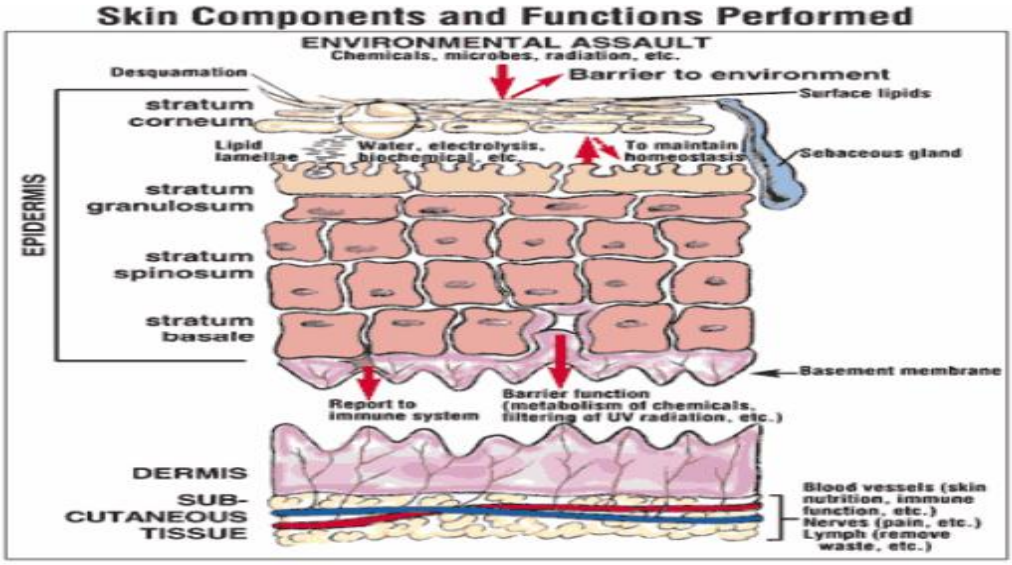
Advantages

- 1. Avoids hepatic first pass metabolism.
- 2. Maintains constant blood levels for longer period of time.
- 3. Improve bioavailability.
- 4. Decrease the dose to be administered.
- 5. Decrease side or unwanted effects.
- 6. Decrease gastrointestinal side effects.
- 7. Easy to discontinue in case of toxic effects.
- 8. Self administration is possible with these systems. Increase patient compliance.

Limitation of TDDS

- Limited skin permeability
- Restricted to potent drug
- Cannot use for large molecule (>500 Dalton)

- Significant lag time
- Skin irritation and allergic response
- Tolerance inducing drugs or those requiring chronopharmacological management is not suitable candidates.
- Cost is high.



ROUTES FOR DRUG PENETRATION THROUGH SKIN

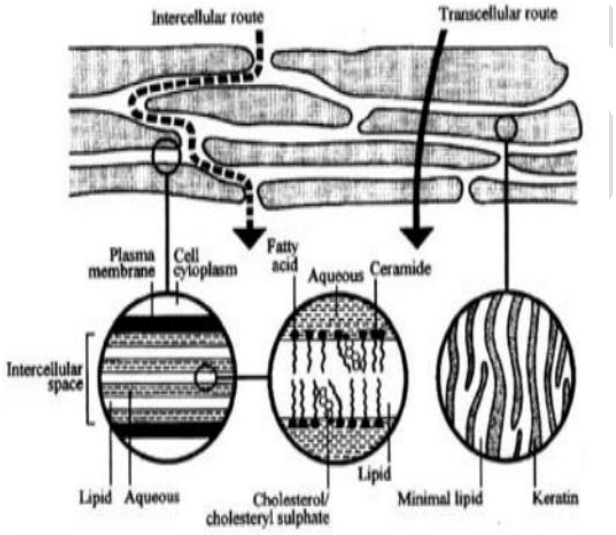
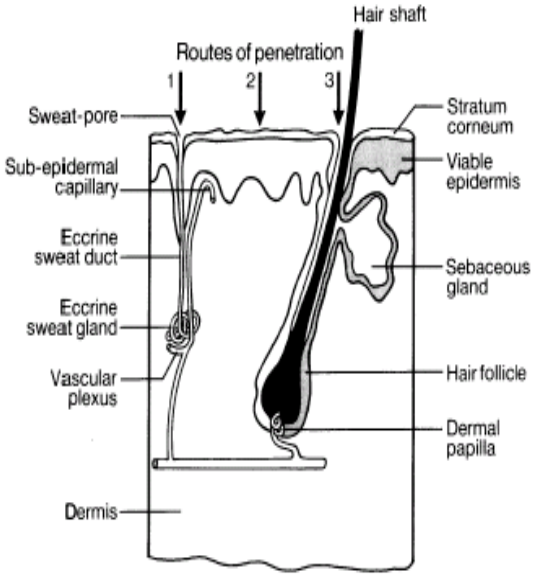


Fig. 2. Simplified diagram of stratum corneum and two microroutes of drug penetration.



Macro Route **Micro Route**

- through the sweat ducts,
- via the hair follicles and
- sebaceous glands
- (collectively called the shunt or appendageal route),
- or directly across the stratum corneum

One Word Question Answer

SR NO.	QUESTION	ANSWER
1	The formulation that is applied to the body surface and is designed to deliver the active drug across the skin, into the systemic circulation, is called?	Transdermal drug delivery system
2	Worldwide market revenues for transdermal products are?	US$3B
3	First development of the modern transdermal is carried out by?	Alza corporation 1970
4	Transdermals deliver drugs from a few hours up to?	7 days
5	Major limitation in TDDS is?	skin permeability
6	Major route of drug penetration through TDDS is?	3

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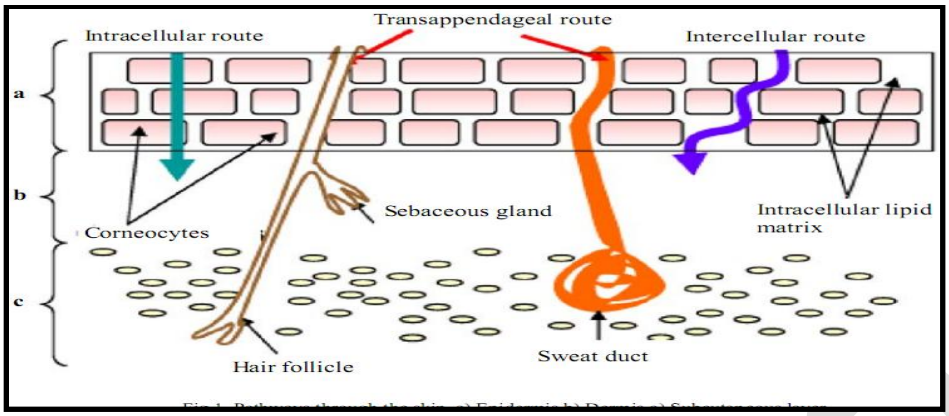
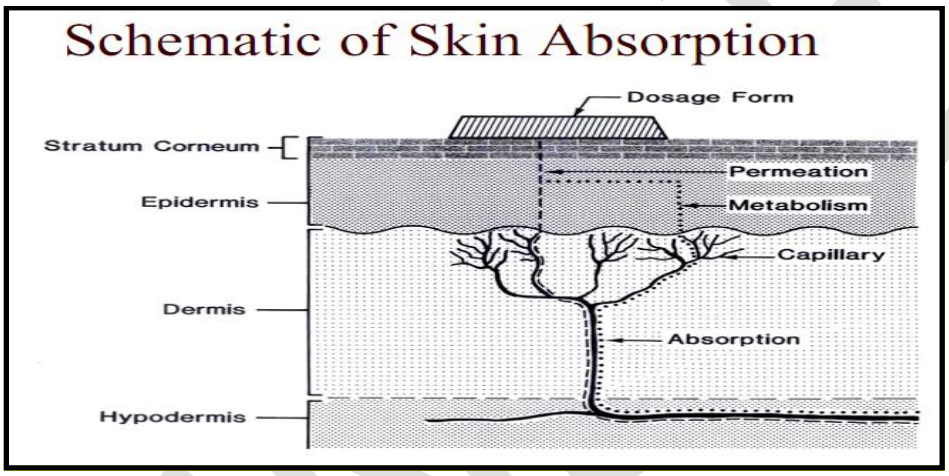


1. Trans cellular penetration (across the cells)

2. Inter cellular penetration (between the cells)

3. Trans appendageal penetration (via hair follicles, sweat and sebum glands, and pilosebaceous apparatus)



- The distance traveled by drug through intercellular or tortous or random pathway is 10 – 20 times higher than that of transcellular route.
- The stratum corneum consists of 10-15 layers of corneocytes and varies in thickness from approximately 10-15 μm in the dry state to40 μm when hydrated.
- It comprises a multi-layered “brick and mortar” like structure of keratin-rich corneocytes (bricks) in an intercellular matrix (mortar) composed primarily of long chain ceramides, free fatty acids, triglycerides, cholesterol, cholesterol sulfate and sterol/wax esters.

FACTORS AFFCETING DRUG PENETRATION

1. The physicochemical nature of the drug particularly size, solubility and partition coefficient
2. The timescale of observation
3. The site and condition of the skin
4. The formulation

5. How vehicle components temporarily change the properties of the stratum corneum

Factors To Be Considered For Transdermal Dose Calculation

Physiochemical	Pharmacokinetic	Biological
Solubility	Half life	Skin toxicity
Crystallinity	Volume of distribution	Site of application
Molecular Weight	Total body clearance	Allergic reactions
Polarity	Therapeutic plasma concentration	Skin metabolism
Melting Point	Bioavailable factor	Skin permeability

IDEAL DRUG CANDIDATE FOR TDDS

1. Must be non-ionic
2. Low molecular weight (less than 500 Daltons)
3. Have adequate solubility in oil and water (log P: 1-3)
4. Low melting point (less than 200 degree C)
5. Dose is less than 50 mg per day, and ideally less than 10 mg per day.

COMPOSITION OF TRANSDERMAL PATCHES

a. Backing films
b. Release liners
c. Pressure-sensitive adhesives
d. Active ingredient(s)
e. Permeation enhancers
f. Other additives
g. Microporous or semi-permeable membranes
h. Pouching materials

i. **Liner -** Protects the patch during storage.
ii. The liner is removed prior to use.
iii. **Drug -** Drug solution in direct contact with release liner
iv. **Adhesive -** Serves to adhere the components of the patch together along with adhering the patch to the skin
v. **Membrane -** Controls the release of the drug from the reservoir and multi-layer patches
vi. **Backing -** Protects the patch from the outer environment

One Word Question Answer

SR NO.	QUESTION	ANSWER
1	Thickness of stratum corneum is?	10-15 µm
2	Which layer of skin contains 10-15 layers of corneocytes?	stratum corneum
3	What is suitable M.W. of drug to prepare TDDS?	less than 500 Daltons
4	What is suitable log p value range of drug to prepare TDDS?	log P: 1-3
5	What is suitable dose of drug to prepare TDDS?	less than 10 mg per day
6	The layer of TDDS that Protects the patch from the outer environment is called?	Backing layer

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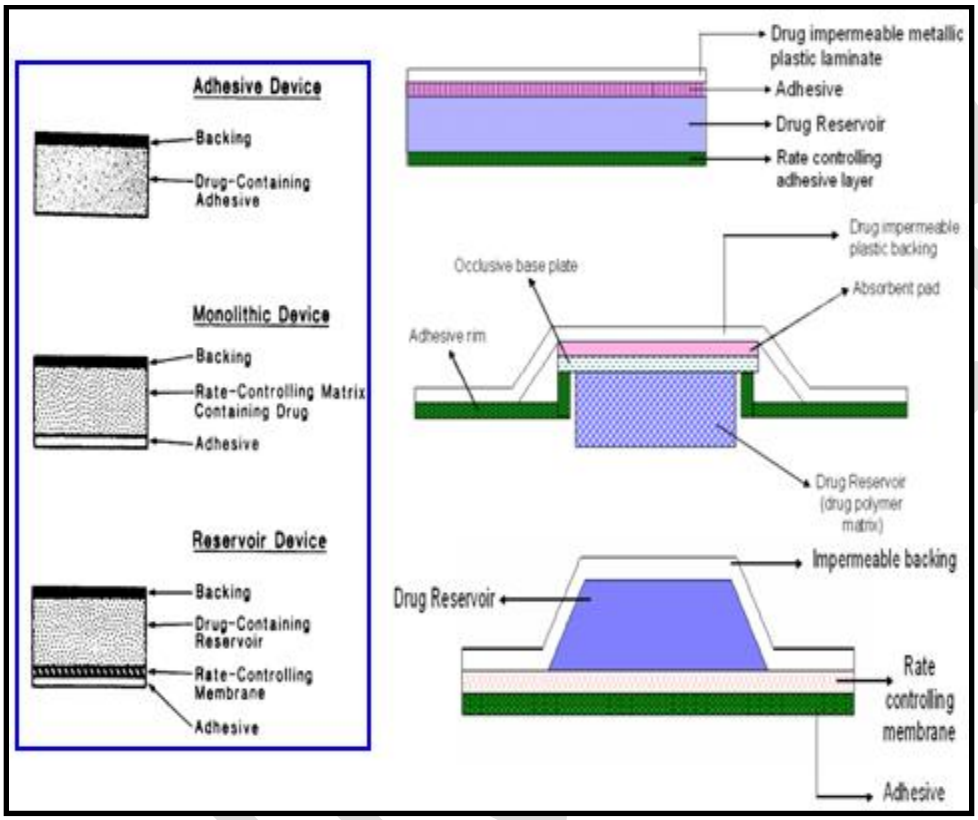
Mechanism Of Action For Percutaneous Absorption Enhancers

1. Reduction of the resistance of the stratum corneum by altering its physicochemical properties.
2. Alteration of the hydration of the stratum corneum.
3. Effecting a change in the structure of the lipids and lipoproteins in the cellular channels, through solvent action or denaturation.
4. Carrier mechanism in the transport of ionizable drugs.



Penetration Enhancers

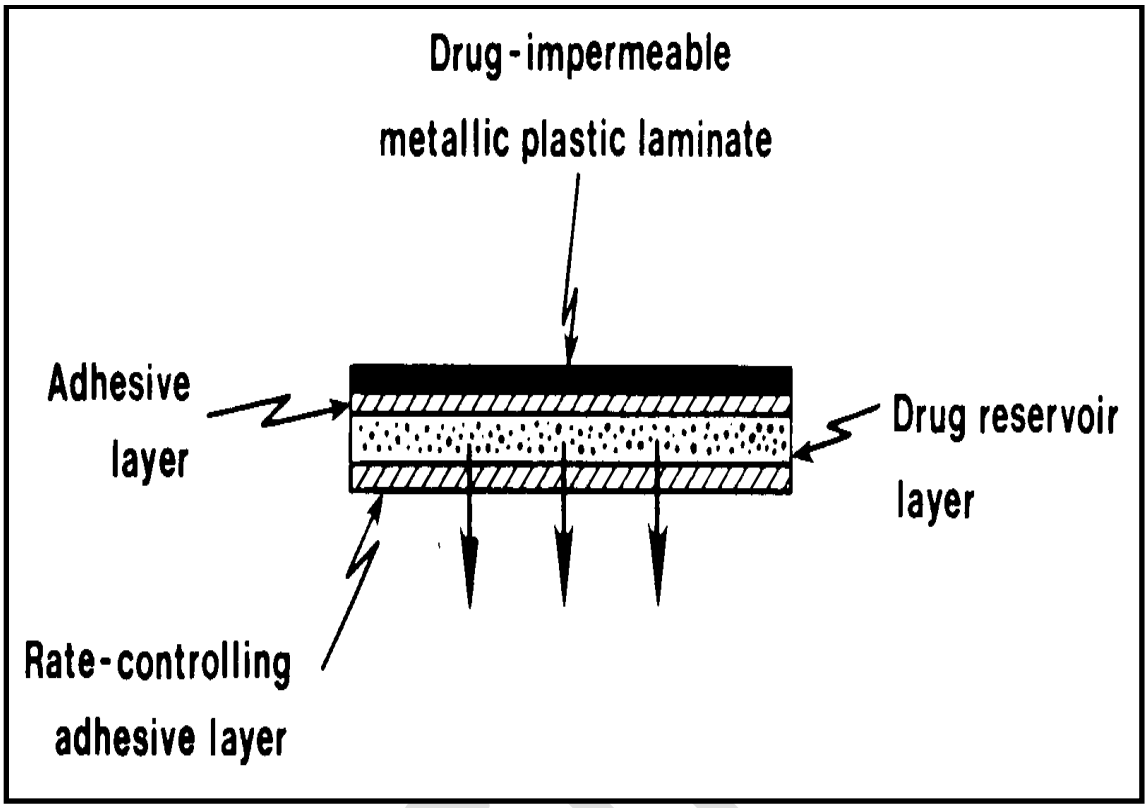
Substance exist which temporarily diminish the impermeability of the skin, known also as accelerants or sorption promoters

Example of Penetration enhancers

Water, Sulphoxides (dimethylsulphoxide), Pyrrolidones, Fatty acids and alcohols, Azone and its derivatives, Surfactants – anonic, cationic and non-ionic, Urea and its derivatives, Alcohols and glycols

APPROACHES TO DEVELOPMENT OF TDDS.

1. Matrix System- Adhesive Diffusion Controlled TDDS
2. Matrix System - Matrix Diffusion Controlled System
3. Reservoir System (Membrane Moderated TDDS):



ADHESSIVE DISPERSION – TYPE SYSTEMS

- The drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated polymer adhesive by solvent casting or by melting the adhesive (in case of hot-melt adhesives) onto an impervious backing layer.
- The drug reservoir layer is then covered by a non-medicated rate controlling adhesive polymer of constant thickness to produce an adhesive diffusion controlling drug delivery
- The rate of drug release in this system is defined by :

$$dQ/dt = K_{a/r} \cdot D_a \cdot C_R / h_a$$

Where,

$K_{a/r}$ = partition coefficients for the interfacial partitioning of the drug from the reservoir layer to adhesive layer.

One Word Question Answer

SR NO.	QUESTION	ANSWER
1	Substance exist which temporarily diminish the impermeability of the skin is called?	Permeation Enhancer
2	Pyrrolidones, Fatty acids are examples of?	Permeation Enhancer
3	How many approaches to develop TDDS?	3
4	The rate of drug release in this system from?	Matrix System- Adhesive Diffusion Controlled TDDS
5	Matrix System- Adhesive Diffusion Controlled TDDS is developed by which method?	Solvent casting method

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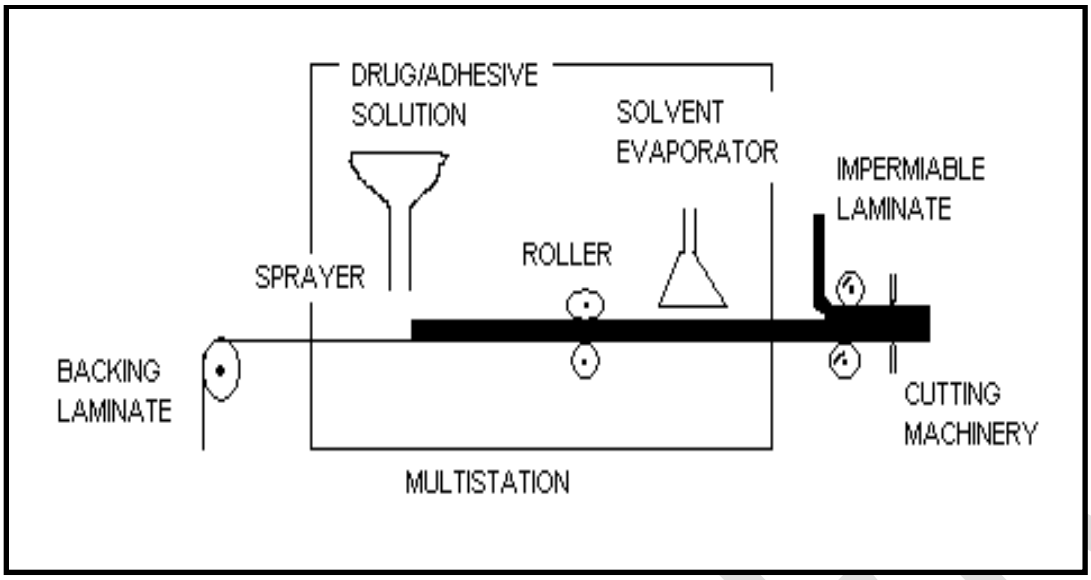
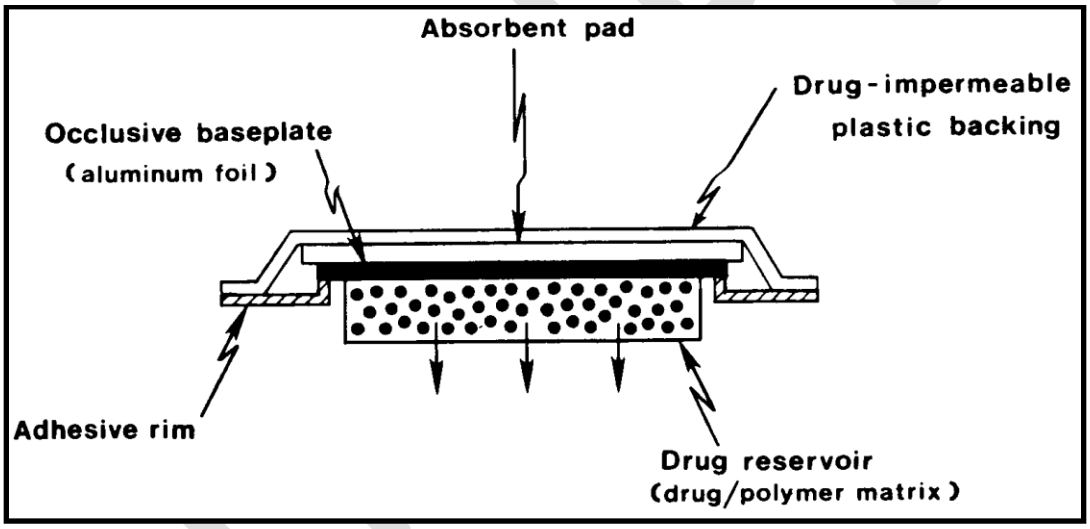


Manufacture of adhesive dispersion type TDDS

MATRIX DIFFUSION - CONTROLED SYSTEMS:

- The drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix.



- This drug containing polymer disk then is fixed onto an occlusive base plate in a compartment fabricated from a drug-impermeable backing layer and surrounded by an adhesive rim.
- The rate of drug release from this type of system is defined as;

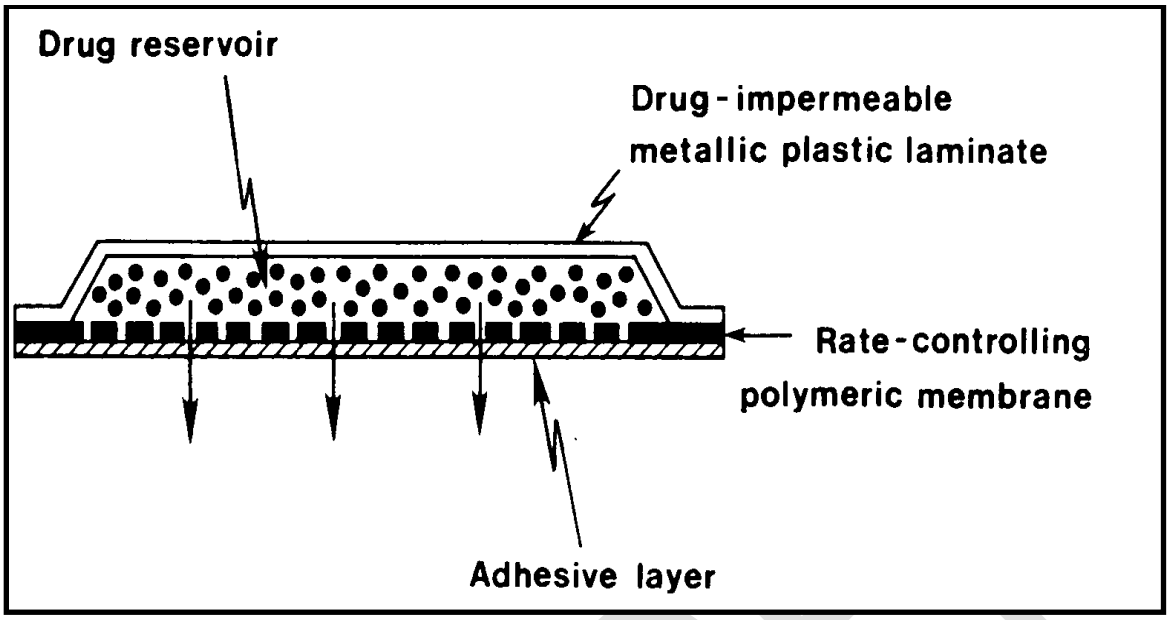
$$\frac{dQ}{dt} = \frac{A\,C_p\,D_p^{1/2}}{2t}$$

Where,

A = Initial drug loading dose dispersed in the polymer matrix.

C_p & D_p = Solubility & Diffusivity of the drug in the polymer.

$C_p = C_R$ (Drug concentration in reservoir compartment)



MEMBRANE PERMEATION – CONTROLLED SYSTEMS:

- The drug reservoir is embedded between an impervious backing layer and a rate controlling membrane.
- The drug releases only through the rate controlling membrane, which can be microporous or non-porous.
- The drug can be in the form of a solution, suspension, or gel or dispersed in solid polymer matrix.
- The intrinsic rate of drug release from this type of drug delivery system is defined by,

  dQ/dt = CR /1/ Pm + 1/ Pa

  Where,

  CR = Drug concentration in the reservoir compartment

  dQ/dt = Rate of drug release from the system

  Pm & Pa = Permeability coefficients of rate controlling membrane and adhesive layer respectively,

One Word Question Answer

SR NO.	QUESTION	ANSWER
1	In which system, the drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix.	Matrix diffusion controlled system
2	Drug-impermeable layer in TDDS is called?	Backing layer
3	$dQ/dt = \frac{A C_p D_p^{1/2}}{2t}$ is equation for?	Matrix diffusion controlled system
4	In which system, the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane?	Matrix permeation-controlled system
5	dQ/dt = CR /1/ Pm + 1/ Pa is equation for?	Matrix permeation-controlled system
6	In which system the drug can be in the form of a solution, suspension, or gel or dispersed in solid polymer matrix.	Matrix permeation-controlled system

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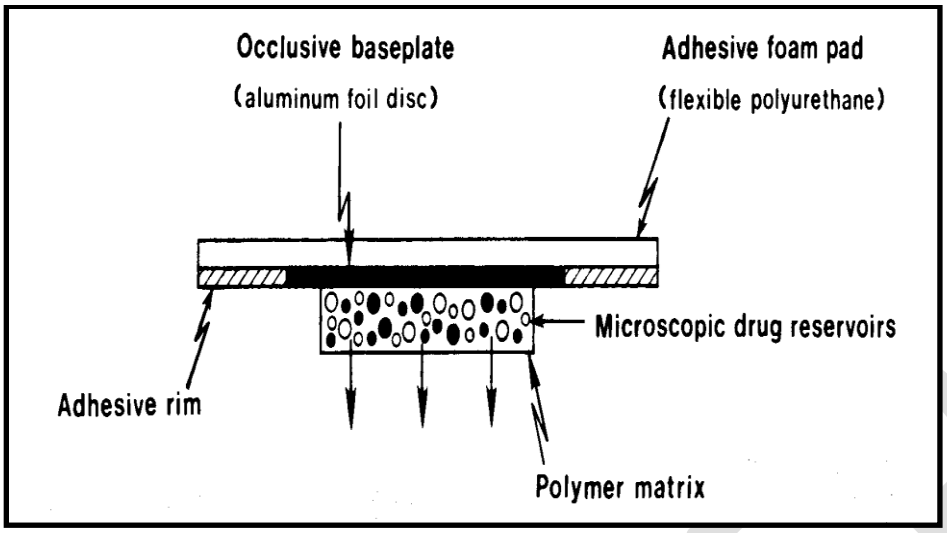


MICRORESERVOIR TYPE systems

- It is a combination of reservoir and matrix-dispersion systems.
- The drug reservoir is formed by first suspending the drug in an aqueous solution of water-soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unleachable, microscopic spheres of drug reservoirs and surrounded by an adhesive rim.
- The rate of release of this system can be defined by,

$$dQ/dt = \frac{D_p \cdot D_d \cdot m \cdot K_p}{D_p \cdot h_d + D_d \cdot h_p \cdot m \cdot K_p} \left[\frac{n \cdot S_p D_1 \cdot S_1 \cdot (1-n)}{h_1} \right] (1/K_1 + 1/K_m)$$

Where,

m = a/b = ratio of drug concentration, in the bulk of the elution medium / outer edge of the polymer.

n = ratio of the drug concentration at the inner edge of the barrier.

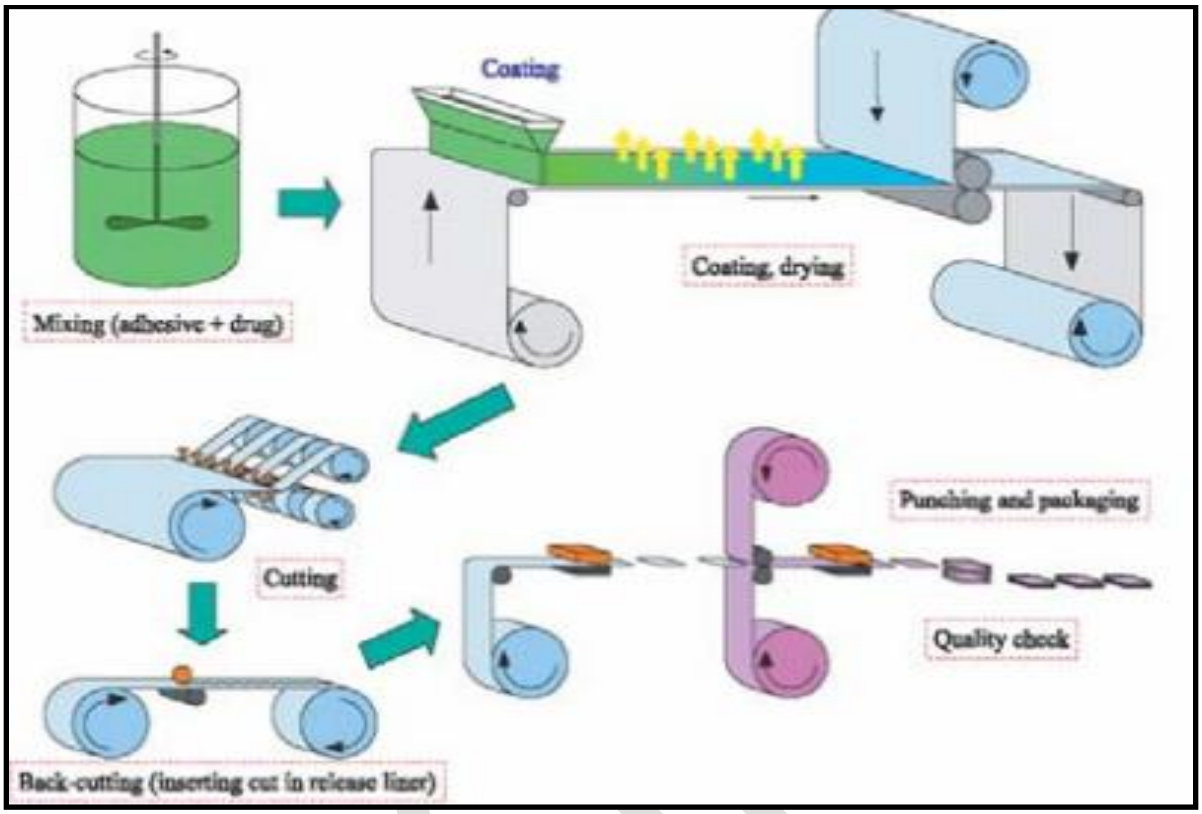
D_1, D_p, D_d = drug diffusivities in liquid layer, polymer layer, and diffusion layer.

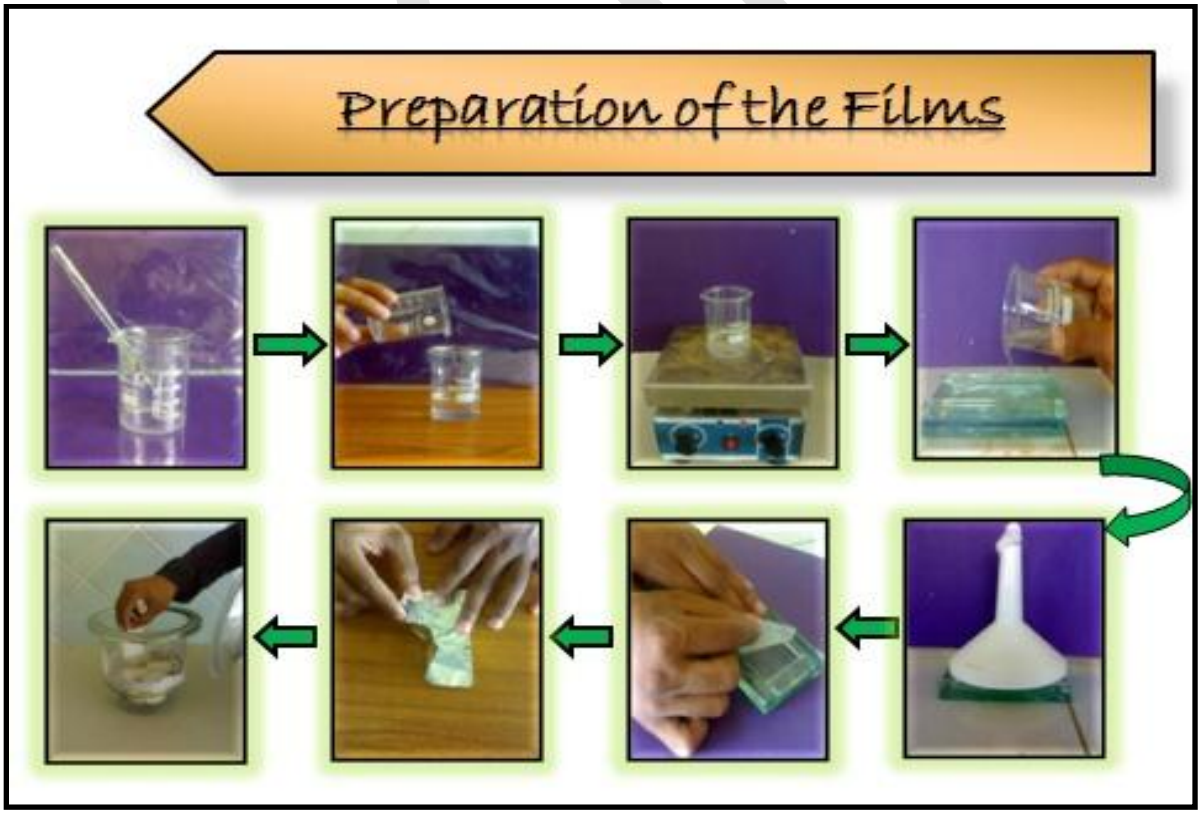
h_1, h_p, h_d = thickness of the layers,

K_1, K_m, K_p = partition coefficients of different layers.

S_1, S_p = solubility's of drug in liquid compartment & polymer matrix.

PREPARATION OF TRANSDERMAL PATCH





One Word Question Answer

SR NO.	QUESTION	ANSWER
1	MICRORESERVOIR system is combination of?	reservoir and matrix-dispersion systems
2	$dQ/dt = \frac{D_p \cdot D_d \cdot m \cdot K_p}{D_p \cdot h_d + D_d \cdot h_p \cdot m \cdot K_p} \left[\frac{n \cdot S_p D_1 \cdot S_1 \cdot (1-n) \quad (1/K_1 + 1/K_m)}{h_1} \right]$ is equation for?	reservoir and matrix-dispersion systems
3	Occlusive base plate contain?	Aluminum foil disk
4	Adhesive foam pad is composed of?	Polythene urethane
5	Microscopic reservoir is surrounded by?	Release linear

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EVALUATION PARAMETERS

Interaction studies -Thermal analysis, FT-IR, UV and chromatographic techniques.

Thickness of the patch –

- using a digital micrometer.

Weight uniformity –

- A specified area of patch is to be cut in different parts of the patch and weigh in digital balance.

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.

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

Percentage moisture uptake = [Final weight- Initial weight/ initial weight] ×100

Water vapour permeability (WVP) evaluation

WVP=W/A

Where, WVP is expressed in gm/m^2 per 24 hrs,

W is the amount of vapour permeated through the patch expressed in gm/24 hrs and A is the surface area of the exposure samples expressed in m^2.

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).

Shear Adhesion test

- An adhesive coated tape is applied onto a stainless steel plate; a specified weight is hung from the tape, to affect it pulling in a direction parallel to the plate.
- Shear adhesion strength is determined by measuring the time it takes to pull the tape off the plate.

Peel Adhesion test

- The force required to remove an adhesive coating form a test substrate is referred to as peel adhesion.

Tack properties

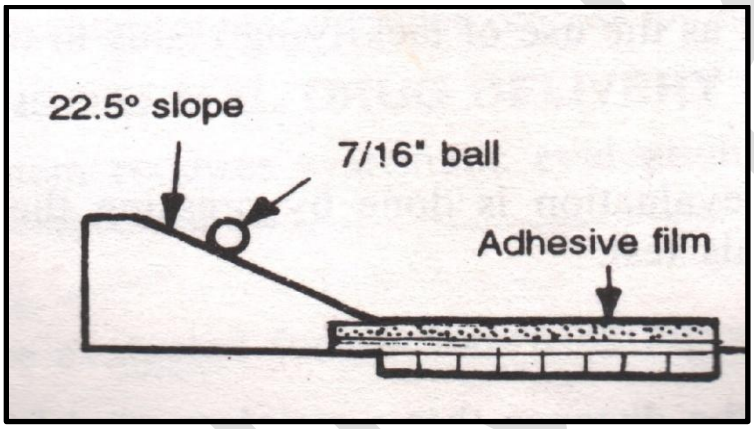
- Tack is the ability of a polymer to adhere to a substrate with little contact pressure.
- It is important in transdermal devices, which are applied with finger pressure.

Thumb tack test

- It is a qualitative test applied for tack property determination of adhesive.
- The thumb is simply pressed on the adhesive and the relative tack property is detected.

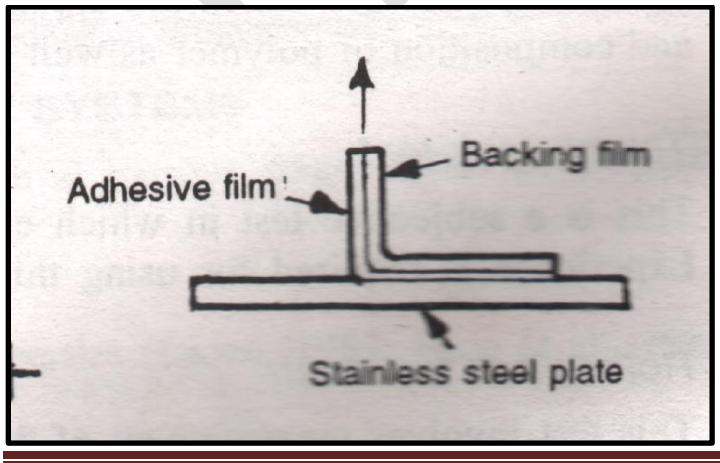
Rolling ball tack test

- It involves measurement of the distance that a stainless steel ball travels along an upward-facing adhesive.
- The less tacky the adhesive, the farther the ball will travel.



Peel tack (or quick-stick) test:

- Peel force required to break the bond between an adhesive and substrate is measured by pulling the tape away from the substrate at 90^0 at a speed of 12 inch/min.



One Word Question Answer

SR NO.	QUESTION	ANSWER
1	Thickness of patch can be measured out by?	digital micrometer
2	The number of times the film could be folded at the same place without breaking gave the value is called?	folding endurance
3	Percentage moisture content equation is?	[Initial weight- Final weight/ Final weight] ×100
4	Water vapour permeability equation is?	WVP=W/A
5	The force required to remove an adhesive coating form a test substrate is referred to as peel adhesion is called?	Peel adhesion test
6	The measurement of the distance that a stainless steel ball travels along an upward-facing adhesive is called?	Rolling ball test
7	Peel force required to break the bond between an adhesive and substrate is measured by pulling the tape away from the substrate at 90^0 at a speed of 12 inch/min is called?	Peel tack test

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***In-vitro* drug release studies**

In-vitro skin permeation studies

- An *in-vitro* permeation study can be carried out by using diffusion cell.

Skin Irritation study

- Skin irritation and sensitization testing can be performed on healthy rabbits.

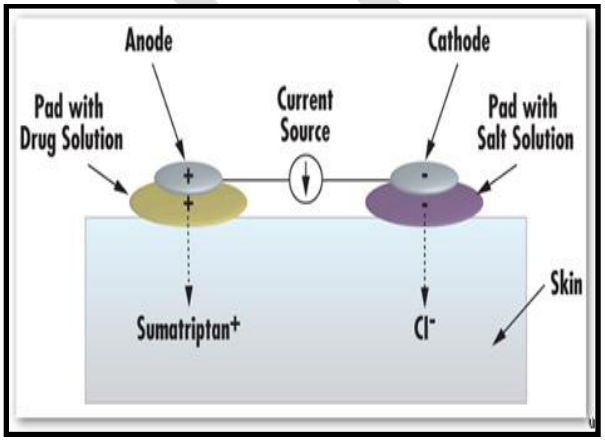
Stability studies

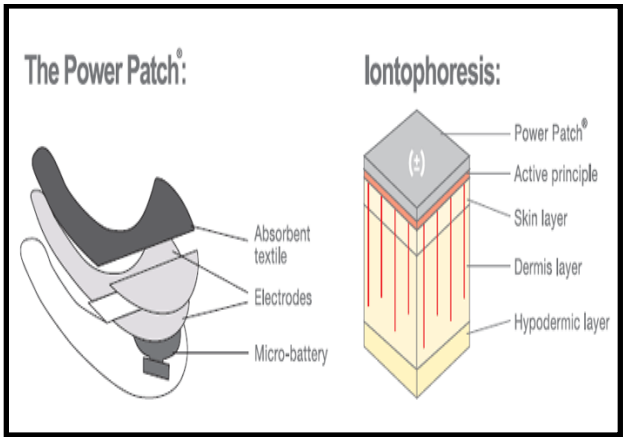
- Stability studies are to be conducted according to the ICH guidelines by storing the TDDS samples at 40±0.5°c and 75±5% RH for 6 months.
- The samples were withdrawn at 0, 30, 60, 90 and 180 days and analyze suitably for the drug content.

Iontophoresis and Sonophoresis

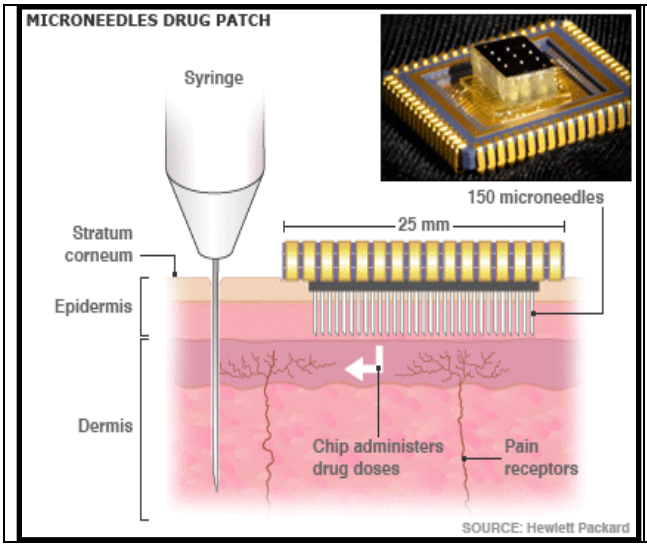
- Iontophoresis involves the delivery of charged chemical compounds across the skin membrane using an applied electrical field.
- Examples: lidocaine, amino acids/peptides/insulin, verapamil, and propanolol **Sonophoresis, or high-frequency ultrasound**, is also being studied as a means to enhance transdermal drug delivery
- Examples: hydrocortisone, lidocaine, and salicylic acid in such formulations as gels, creams and lotions

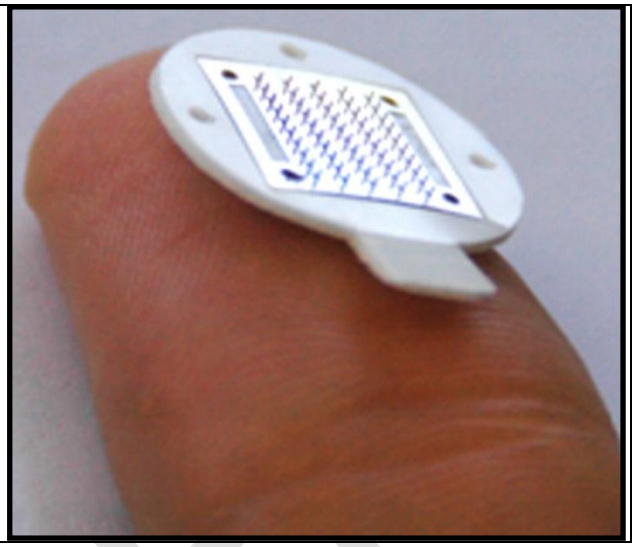
Iontophoretic Patches





Microneedles Patches





Examples

- **Hormone replacement. (Testosterone, ERT, HRT,)**
- **Angina. (Nitroglycerin)**
- **Pain relief. (Fentanyl)**
- **Hypertension. (Clonidine)**
- **Motion sickness. (Scopolamine)**
- **Smoking cessation. (Nicotine)**
- **Depression. (Selegiline)**

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One Word Question Answer

SR NO.	QUESTION	ANSWER
1	which qualitative test is applied for tack property determination of adhesive	Thumb tack test
2	An *in-vitro* permeation study can be carried out by?	Franz diffusion cell
3	Skin irritation and sensitization testing can be performed on?	Healthy rabbits
4	Stability studies are to be conducted according to?	ICH guidelines
5	The samples were withdrawn at how many days?	0, 30, 60, 90 and 180 days
6	Which technique involves the delivery of charged chemical compounds across the skin membrane using an applied electrical field?	Iontophoresis

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