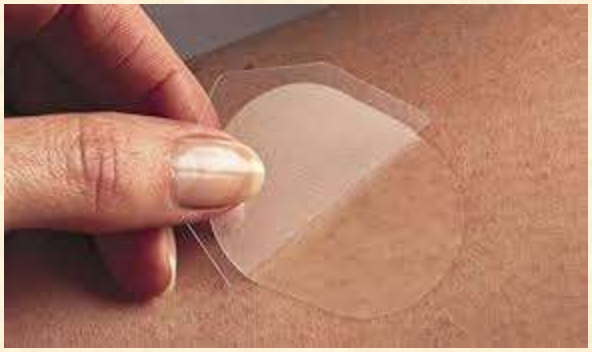
# TRANSDERMAL DRUG DELIVERY,

# IONOTOPHORESIS

# &

# SONOPHORESIS



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# Definition:

Self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at controlled rate to the systemic circulation

## *Advantages :*

- Delivers a steady infusion of a drug over an extended period of time.
- Increase the therapeutic value of drug by avoiding specific problems associated with the drug.
- An equivalent therapeutic effect can be elicited via transdermal drug input with a lower daily dose of the drug than is necessary e.g., as the drug is given orally.
- Improved patient compliance due to simplified medication regimen and reduced inter and intra –patient variability
- Self administration is possible
- Drug input can be terminated at any point of time by removing transdermal patch

# Disadvantages :

- The drug must have some desirable physicochemical properties for penetration through stratum corneum. Daily doses of less than 5mg/day are preffered
- Skin irritation or contact dermatitis due to the drug, excipients and percutaneous absorption enhancers.
- The barrier function of skin changes from one site to another on the same person, from person to person and with age.

# Kinetics of transdermal permeation :

- Permeation of drug involves the following steps:
  i. Sorption by stratum corneum
  ii. Penetration of drug through viable epidermis
  iii. Uptake of the drug by the capillary network in the dermal papillary layer

- Rate of permeation across skin:

$$\frac{dQ}{dt} = P_s (C_d - C_r)$$

Where,

$\mathbf{C_d}$, $\mathbf{C_r}$ = concentrations of skin penetrant in donor (side of stratum corneum) and receptor compartment (body) respectively

$\mathbf{P_s}$ = permeability coefficient of skin tissues to drug = $\frac{K_{ss} D_{ss}}{h_s}$

$\mathbf{K_{ss}}$ = Partition coefficient, $\mathbf{D_{ss}}$ = apparent diffusivity for the steady-state diffusion

$\mathbf{h_s}$ = overall thickness of skin tissues

- Constant rate of drug obtained can be obtained only when $C_d >>> C_r$

  Therefore, $\frac{dQ}{dt} = P_s C_d$

- Rate of skin permeation is constant if $C_d$ is constant throughout the course of skin permeation. To maintain this, rate of drug release ($R_r$) must be greater than rate of skin uptake ($R_a$)

- ❑ Therefore, maximum rate of skin permeation, $(dQ/dt)m = P_s C_s$

- ❑ Thus, skin permeation appears to be stratum corneum-limited

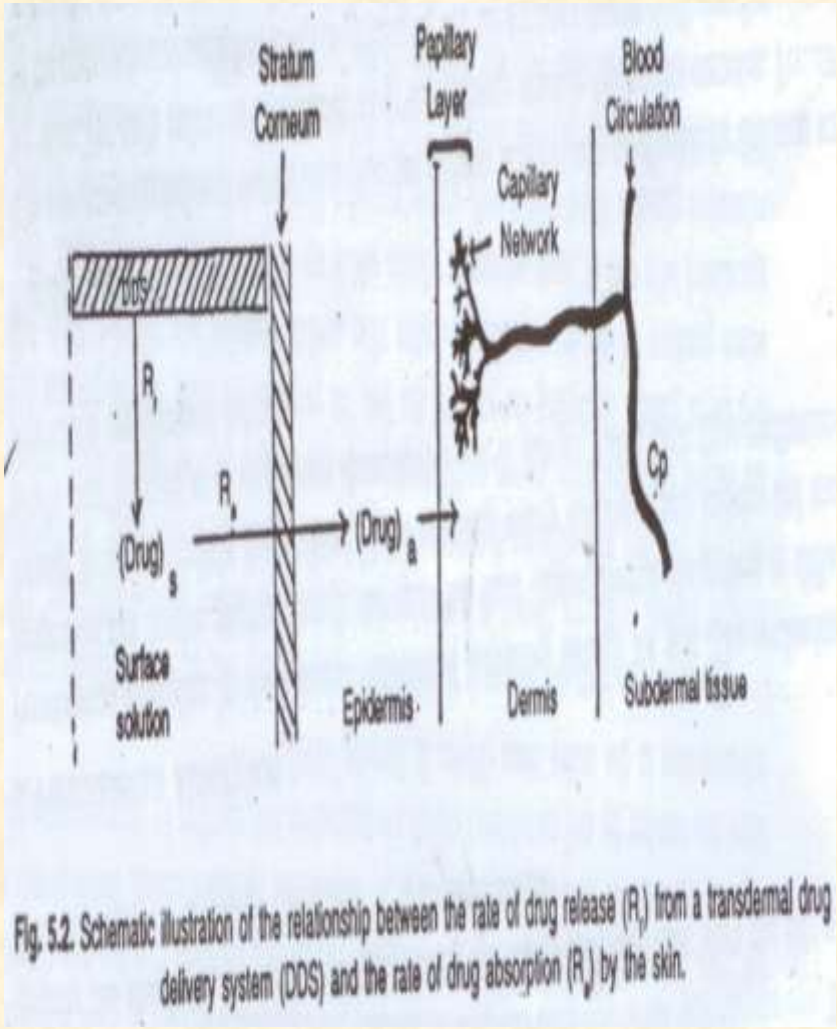



Fig. 5.2. Schematic illustration of the relationship between the rate of drug release ($R_r$) from a transdermal drug delivery system (DDS) and the rate of drug absorption ($R_a$) by the skin.

# Basic components of TDDS:

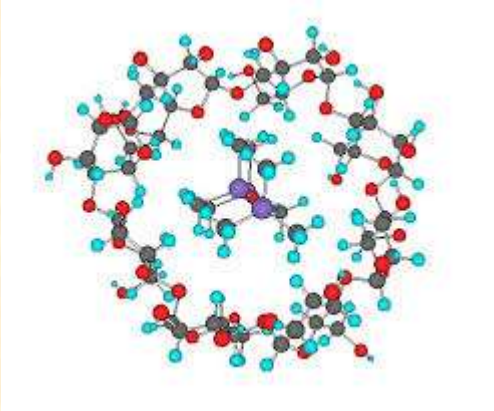
1) Polymer matrix or matrices

1) The drug

2) Permeation enhancers

3) Other excipients

# Polymer matrix or matrices



- Possible useful polymers for transdermal devices:

❖ Natural polymers:-

cellulose derivatives, Zein, waxes, proteins, gums and their derivatives, natural rubber, starch

❖ Synthetic elastomers:-

Polybutadiene, Hydrin rubber, polysiloxane, Nitrile, Acrylonitrile, Styrene, Neoprene etc.

❖ Synthetic pulymers:-

Polyvinyl alcohol, Polyethylene, Polyacrylate, Polyvinylpyrrolidonr, Polymethylmethacrylate, Epoxy etc.

# Drug :

## Physicochemical properties:

- Molecular weight less than approximately 1000 daltons
- Should have affinity for both lipohilic and hydrophilic phases. Extreme partitioning characteristics are not conductive to successful drug delivery via skin.
- Drug should have low melting point.

## Biological properties:

- Should be potent with a daily dose of the order of a few mg/day.
- Half-life of the drug should be short
- Must not induce cutaneous irritant or allergic response.
- Drugs which degrade in the GI tract or are inactivated by hepatic first-pass effect are suitable candidates for transdermal delivery
- Drugs which have to be administered for a long period of time or which cause adbverse effects to non-target tissues can also be formulated for transdermal delivery.

# Permeation enhancers

- These are the compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant

- The flux J across the skin:

$$J = D \frac{dc}{dx}$$

Where,

D = diffusion coefficient

C = concentration of diffusing species

X = spatial coordinate

# Classification

| S.NO | TYPE | MECHANISM | EXAMPLES |
|---|---|---|---|
| 1. | Solvents | Increase penetration possibly by swelling the polar pathway and/or by fluidizing lipids. | water alcohols, alkyl methyl sulfoxides, pyrrolidones |
| 2. | Surfactants | Enhance polar pathway transport, especially of hydrophilic drugs | **Anionic surfactants**:- Dioctyl sulfosuccinate, sodium lauryl sulphate<br>**Nonionic surfactants**:- Pluronic F127, Pluronic F68 etc.<br>**Bile salts**:- Sodium taurocholate, sodium deoxycholate |
| 3. | Binary systems | These systems apparently open up the heterogenous multilaminate pathway aswell as the continate pathway | propylene glycol-oleic acid & 1,4-butane diol-linoleic acid |
| 4. | Miscellaneous chemicals | Hydrating and keratolytic agent | •N,N-dimethyl-m-toluamide<br>•Recently described:- eucalyptol, di-o-methyl-β-cyclodextrin |

## *Adhesives :-*

✓Fastening of the transdermal devices to skin has been done by using a pressure sensitive adhesive

✓pressure sensitive adhesive can be positioned on the face of the device or in the back of the device and extending peripherally.

**Criteria for face adhesive system**

➢Permeation of drug should not be effected

➢Delivery of simple or blended permeation enhancers should not be affected

➢e.g., polyisobutylenes, acrylics and silicones

## *Backing membrane:*

•Flexible, provide good bond to the drug reservoir, prevent drug from leaving the dosage form through the top

•e.g., metallic plastic laminate, plastic backing with absorbent pad and occlusive base plate (aluminium foil), adhesive foam pad (flexible polyurethane) with occlusive base plate (aluminium foil disc) etc.

# *Approaches used in development of transdermal drug delivery systems*

**Four different approaches have been used**

1) Membrane permeation – controlled systems

2) Adhesive dispersion – type systems

3) Matrix diffusion – controlled systems

4) Microreservoir type or microsealed dissolution controlled systems

# Membrane permeation – controlled systems

- Constant release rate of drug is the major advantage
- A rare risk-- Accidental breakage of the rate controlling membrane can result in dose dumping or a rapid release of the entire drug content.
- Intrinsic rate of drug release:

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

- Pm = permeability coefficient of rate controlling membrane = $\frac{K_{m/r} \cdot D_m}{h_m}$
- Pa = permeability coefficient of adhesive layer

$$= \frac{K_{a/m} \cdot D_m}{h_m}$$

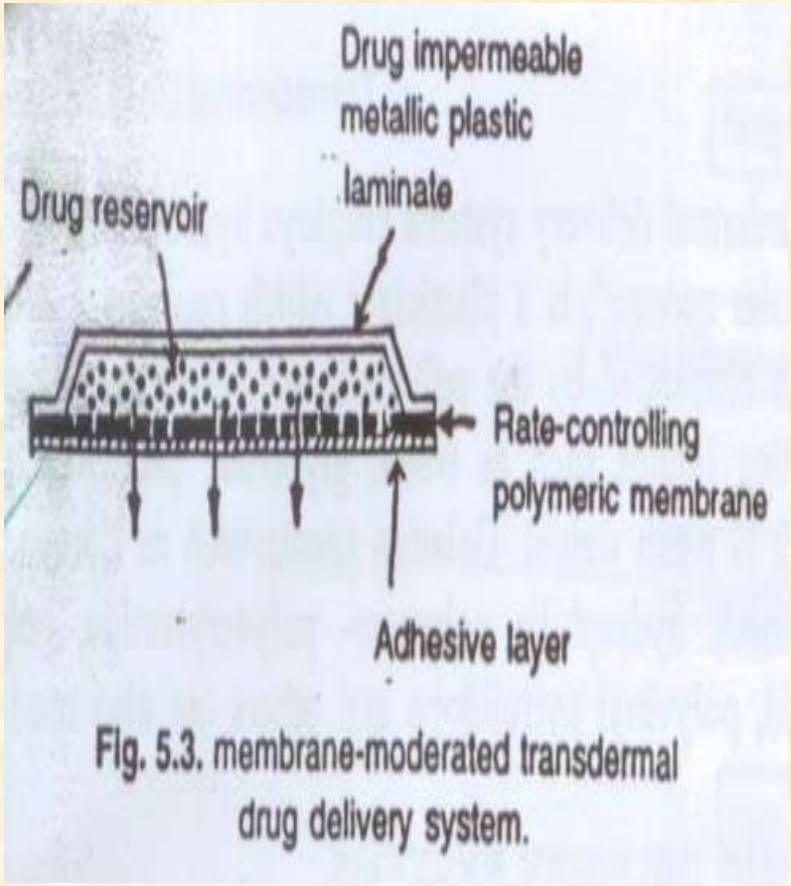



Fig. 5.3. membrane-moderated transdermal drug delivery system.

# Adhesive dispersion – type systems

- The rate of drug release is defined by:

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

Where,

$K_{a/r}$ = Partition coefficient for the interfacial partitioning of the drug from the reservoir layer to adhesive layer

Example:

Isosorbide dinitrite – releasing transdermal therapeutic system

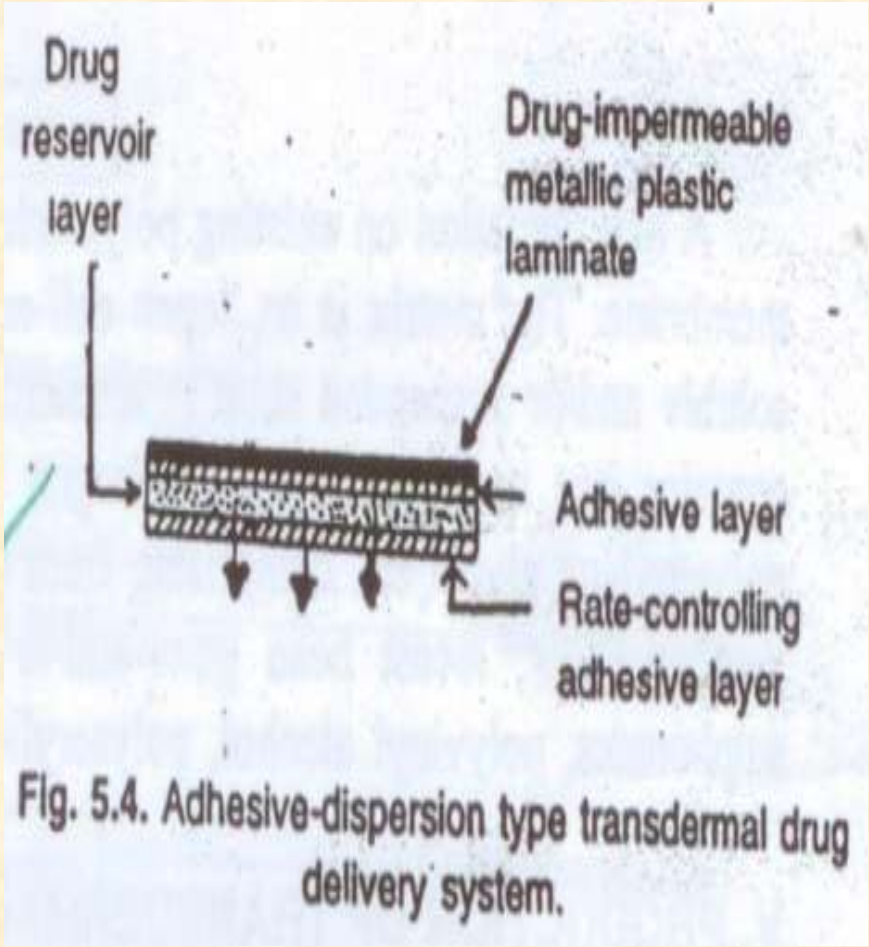



Fig. 5.4. Adhesive-dispersion type transdermal drug delivery system.

# Matrix diffusion – controlled systems

**Example:**

- Nitroglycerine – releasing transdermal therapeutic system

- These are designed to be applied to the intact skin to provide a continuous transdermal infusion of nitroglycerine for therapy of angina pectoris

**Advantage:-** Absence of dose dumping

- The rate of drug release is defined by:

$$\frac{dQ}{dt} = \left[\frac{AC_p\ D_p}{2t}\right]^{1/2}$$

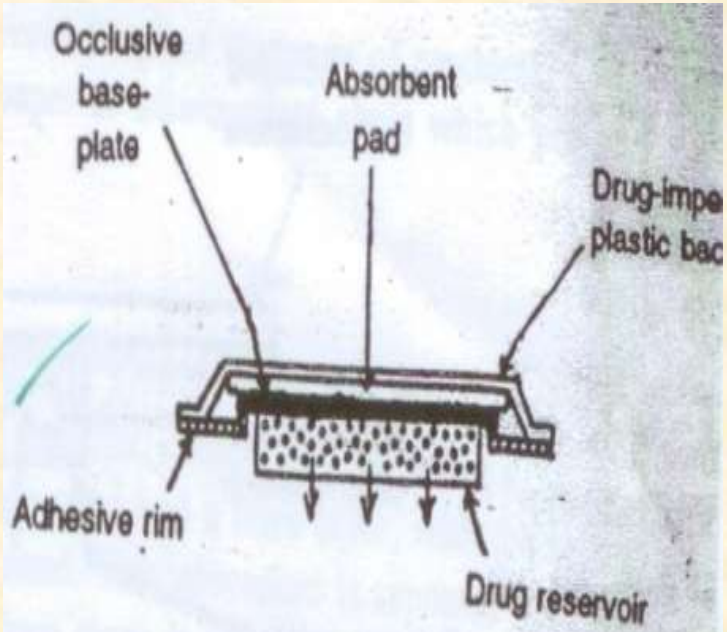



Fig. 5.6. Cross-sectional view of matrix diffusion co transdermal drug delivery system showing maj structural components.

# Microreservoir type or microsealed dissolution controlled systems

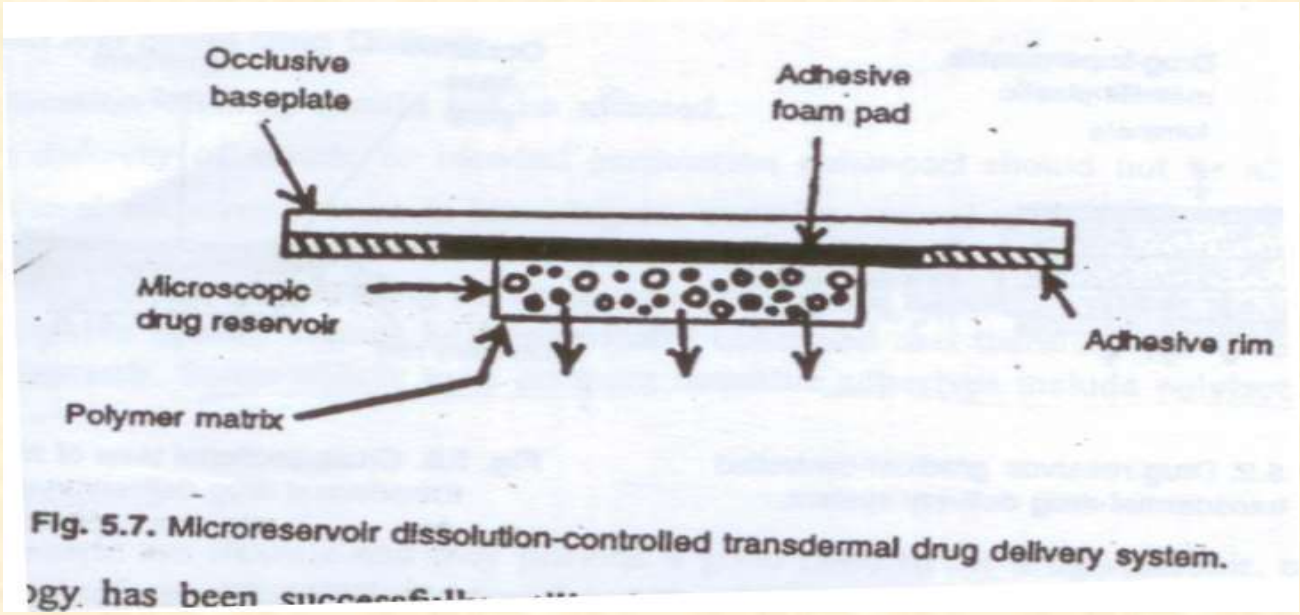



Fig. 5.7. Microreservoir dissolution-controlled transdermal drug delivery system.

ogy has been

**Example:**

Utilised in the preperation of nitrodisc, a nitroglycerine releasing transdermal therapeutic system.

- The release rate of drug is defined by:

$$\frac{dQ}{dt} = \left[ n.S_p \frac{D_1.S_1(1-n)}{h_1} \left\langle \frac{1}{K_1} + \frac{1}{K_m} \right\rangle \right]$$

Where,

**m**= a/b. **'a'** is the ratio of drug concentration in the bulk of the elution medium over drug solubility in the same medium.

**'b'** is the ratio of drug concentration at the outer edge of the polymer coating over drug solubility in the same polymer composition.

**n** = ratio of drug concentration at the inner edge of the interfacial barrier over drug solubility in the polymer matrix

**$D_1$,$D_p$,$D_d$** = drug diffusivities in the liquid layer surrounding the drug particles, polymer coating membrane surrounding the polymer matrix and the hydrodynamic diffusion layer surrounding the polymer coating with respective thickness of $h_1$,$h_p$&$h_d$

**$K_1$,$K_m$,$K_p$** = partition coefficients for the interfacial partitioning of the drug from the liquid compartment to the polymer matrix, from the polymer matrix to the polymer coating membrane and from polymer coating to the elution solution.

**$S_1$,$S_p$** = solubilities of the drug in the liquid compartment and in the polymer matrix.

# Evaluation of TDDS

## 1. Evaluation of adhesive:

### a) Peal adhesion properties:

- Peel adhesion is the force required to remove an adhesive coating from a test substrate
- It is affected by molecular weight of adhesive polymer, type and amount of additives, and polymer composition.
- Test:
- The test invovles measuring the force required to pull a single coated tape, applied to substrate at a $180^0$ angle.
- No residue on substrate indicates “adhesive failure”
- Remnants on substrate indicates “cohesive failure”

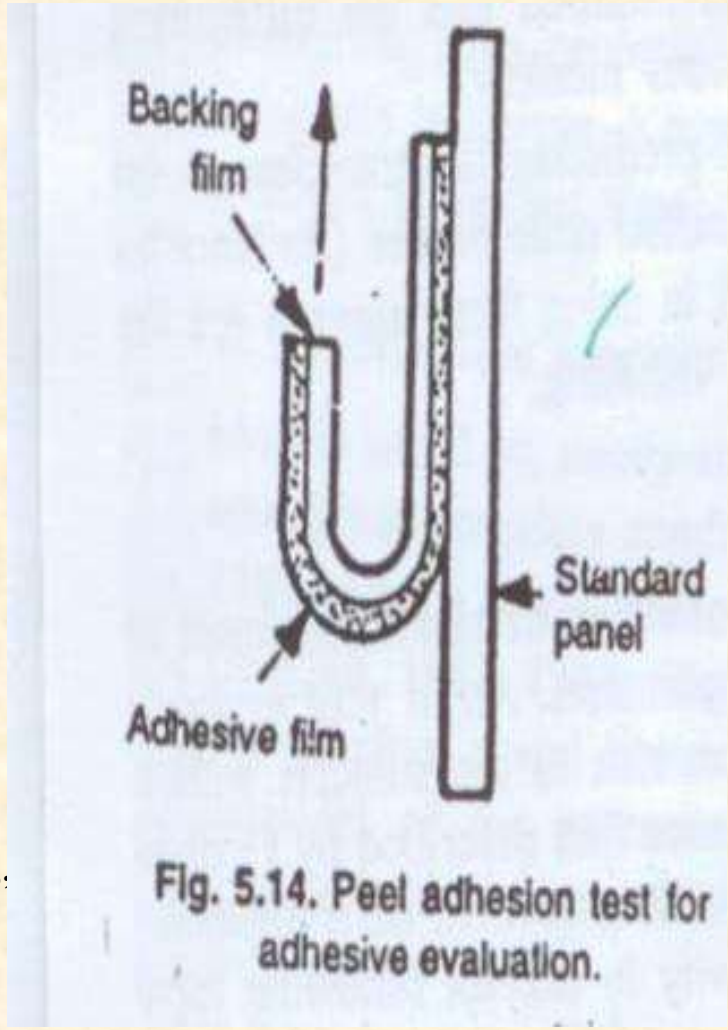



Fig. 5.14. Peel adhesion test for adhesive evaluation.

## b) Tack properties:

- Ability of polymer to adhere to a substrate with little contact pressure
- Affected by molecular weight and compostion of polymer, tackifying resins in the polymer.
- **"Thumb tack test"** – measured by pressing the thumb briefly into the adhesive layer
- **"Rolling ball tack test"** – measurement of distance that a stainless steel ball travels along an upward placed adhesive.
- **"Quick-stick test (peel tack test)" –** pulling the tape away from substrate at $90^0$ at a speed of 12inch/min
- **"Probe tack test"** – force required to pull a probe away from adhesive at a fixed rate is recorded as tack

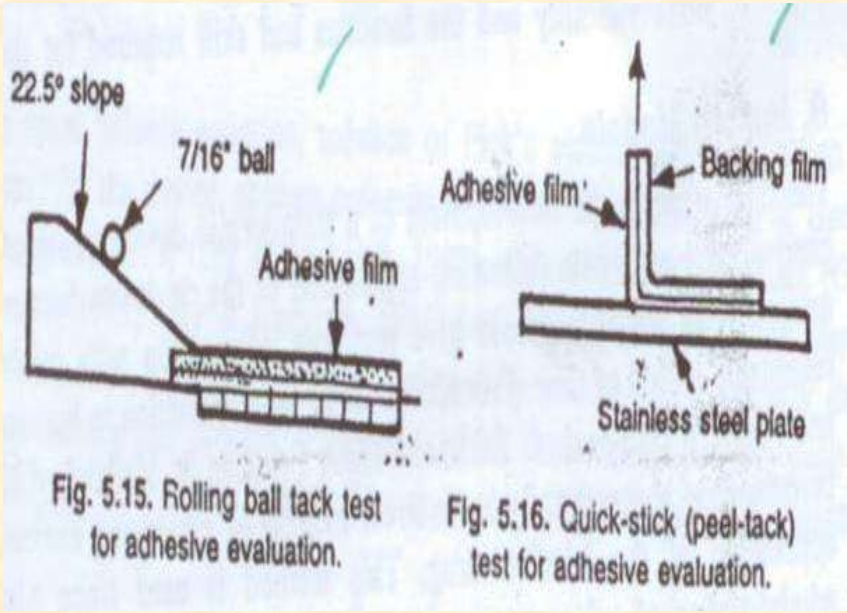



Fig. 5.15. Rolling ball tack test for adhesive evaluation.

Fig. 5.16. Quick-stick (peel-tack) test for adhesive evaluation.

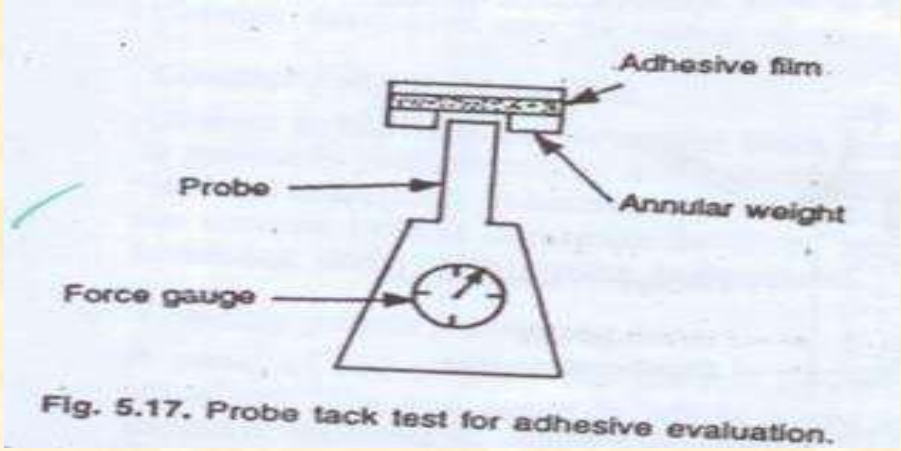


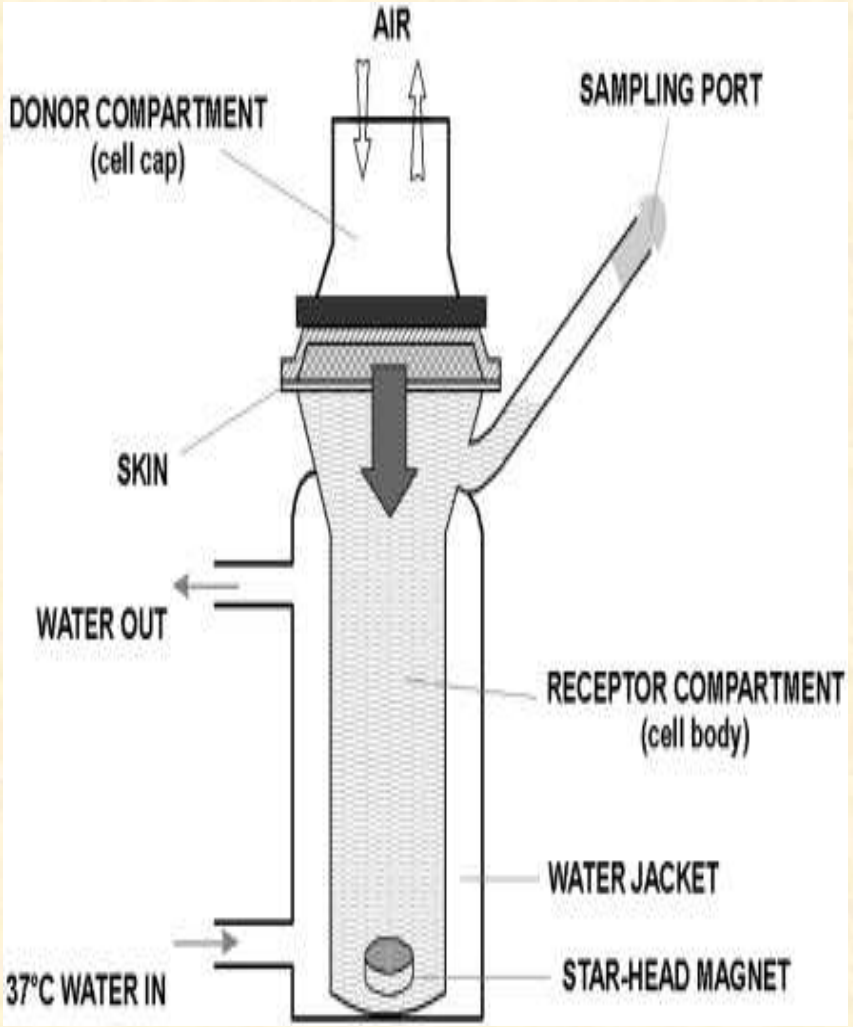

Fig. 5.17. Probe tack test for adhesive evaluation.

## 2. *Invitro* drug release evaluation

- Help in vestigating mechanism of skin permeation before developing a TDDS.
- Studies on skin metabolim can also be performed

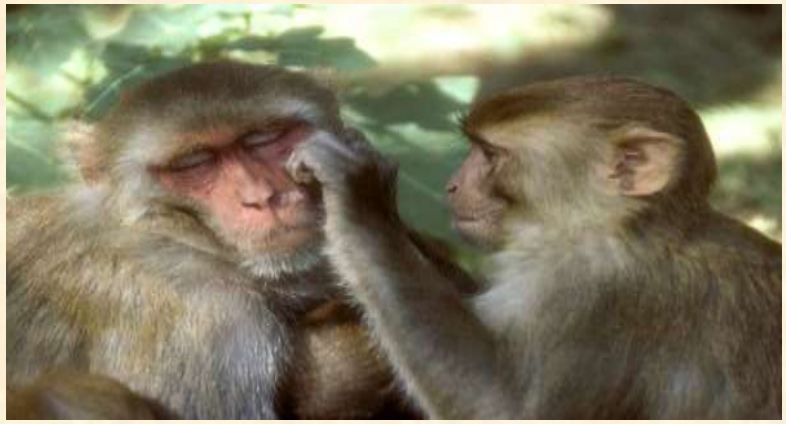
Advantages:

- Methodology
- Ease of analytical assay since there are no complications arising from disposition of drug in the body
- Better control of experimental conditions than in invivo




FRANZ DIFFUSION CELL

# 3.*Invivo* evaluation:



## a) Animal models:

i. Penetration values obtained with small hairy animals are higher than those seen in man. Preparation of their skin for study, by shaving or depilation lead to changes in resistance.

ii. Rhesus monkey is the most reliable model. Limtation of using this animal:- cost, handling capabilities, difficulty of accessibility and ethical considerations

iii. Other animals used:- weanling pig, human skin grafted-nude mouse

## b) Human models

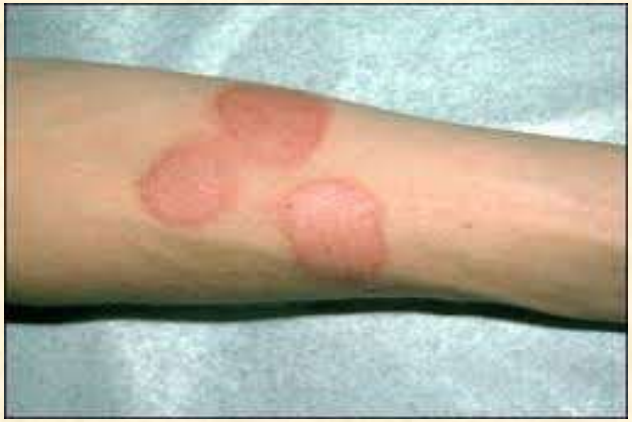
- Percutaneous absorption determined by indirect method:- measuring radioactivity of excreta following topical application of the labelled drug

$$\% \text{ dose absorbed} = \frac{\text{Total radioactivity excreted after topical administration}}{\text{Total radioactivity excreted after Intravenous administration}} \times 100$$

- "Reservoir technique" :- to overcome the inherent limitations in above process
- Short exposure of skin to the radiolabelled drug followed by removal of stratum corneum.

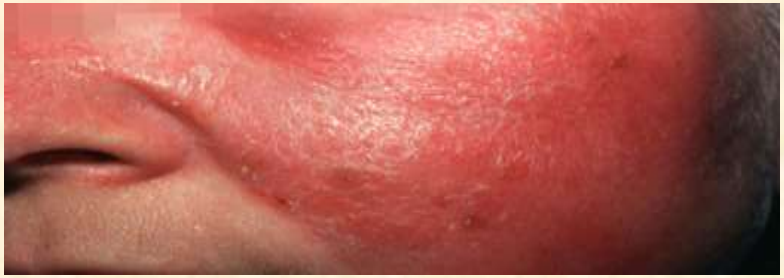
## c) Biophysical models

# 5. Cutaneous toxicological evaluations



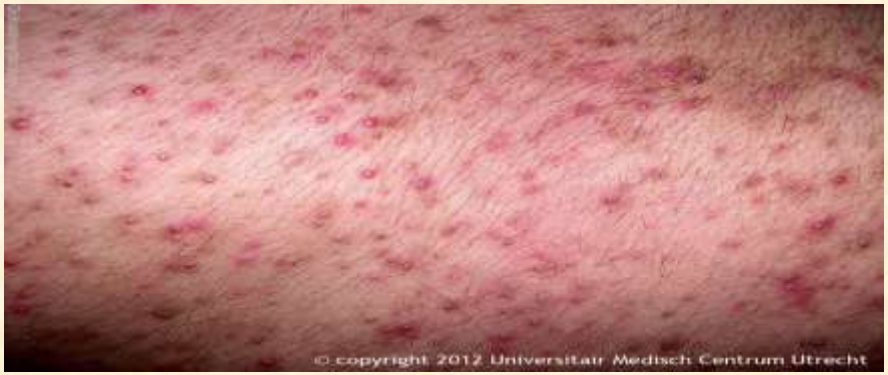
a) Contact dermatitis

- ❖ Contact irritant dermatitis
  - Ten day primary irritation test
  - Twenty one day irritation test
    - ➢ Laser doppler
    - ➢ Evaporative water loss measurements
- ❖ Contact allergic dermatitis



b) Growth of microorganisms

- ❖ Localised superficial infections
- ❖ Miliaria



## IONTOPHORESIS

Definition: Iontophoresis can be defined as the permeation of ionized drug molecules across biological membranes under the influence of electric current.

## SONOPHORESIS

Definition: Sonophoresis is the enhancement of migration of drug molecules through the skin by ultrasonic energy

| Sr no | Sonophoresis | Iontophoresis |
|---|---|---|
| 1 | Sonophoresis is the enhancement of migration of drug molecules through the skin by ultrasonic energy | Iontophoresis is movement of ions of soluble salts across a membrane under an externally applied potential difference |
| 2 | Sonophoresis uses acoustic energy (ultrasound) to drive molecules into tissues | Iontophoresis uses electiral current to transport ions into tissues |
| 3 | Proper choice of ultrasound parameters including ultrasound energy dose, frequency, intensity, pulse length, and distance of transducer from the skin is critical for efficient sonophoresis. | Proper choice of electricity parameters including Current density, Current profile, Duration of treatment, Electrode material, Polarity of electrodes, is critical for efficient Iontophoresis |
| 4 | Sonophoresis usually employs a ultrasound between 20 KHz to 20 MHz | Iontophoresis usually employs a direct current between 0.5 mA to 5.0 mA |

| | | |
|---|---|---|
| 5 | In sonophoresis drugs mixing with a coupling agent like gel, cream, ointment | In Iontophoresis drug is mix with solvent |
| 6 | The main mechanism for transport of drug is “Cavitation” | The main mechanism for transport of drug is “Electroporation” |
| 7 | Drug should be in aqueous or non aqueous and ionized or non ionized form | Drug must be in aqueous and must be in ionized form |
| 8 | Enhanced partitioning, Lipid bilayer disordering, Keratin denaturation etc. gives the synergetic effect of sonophoresis | Electrophoresis, Lipid bilayer disordering, Electroosmosis etc. gives the synergetic effect of Iontophoresis |
| 9 | Ultrasound can be applied in a continuous or pulse mode | Electrical current can be applied only in continuous mode |
| 10 | Sonophoresis mostly used for delivery of corticosteroids, local anesthetics and salicylates | Iontophoresis mostly used for hyperhydrosis diagnosis of cystic fibrosis, metallic and non-metallic ions |

# REFERENCES


- Controlled and Novel Drug Delivery by N.K. Jain, Pg. No : 100 to 127, 191 to 206 and 207 to 233.

- Ionotophoreseis : A novel approach to transdermal drug delivery, Pharma buzz, November 2007, Vol 2/ Isuue 11


Thank You!