TRANSDERMAL DRUG DELIVERY

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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 e.g., gastro-intestinal irritation, low absorption, decomposition due to hepatic "first-pass" effect, formation of metabolites that cause side effects, short half-life necessitating frequent dosing etc.
- 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,

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

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

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

h_s = overall thickness of skin tissues

Kinetics of transdermal permeation

- 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

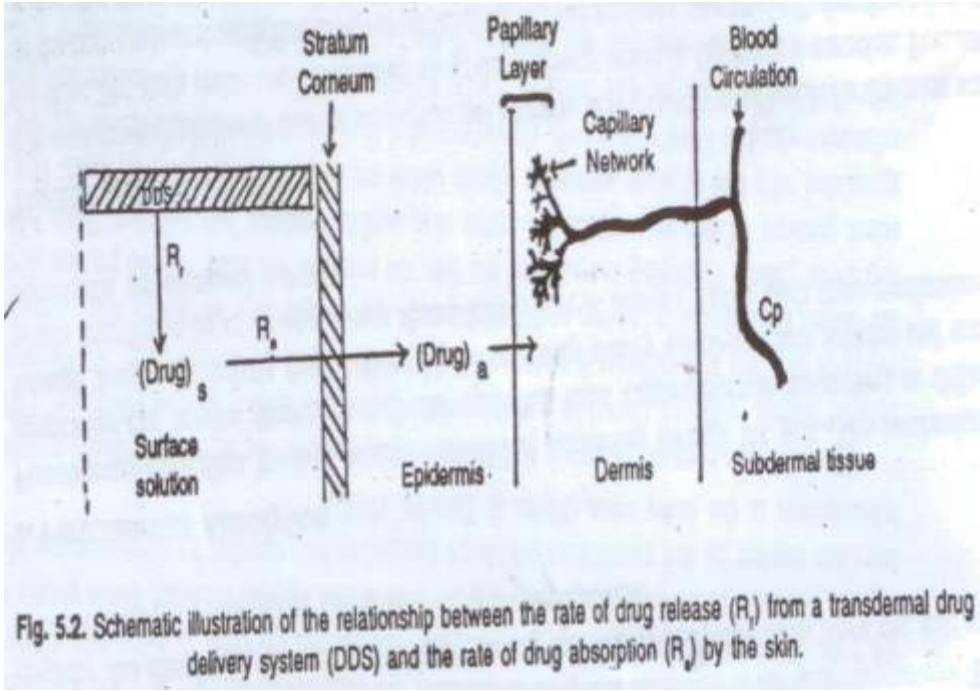

Fig. 5.2. Schematic illustration of the relationship between the rate of drug release (R_r) from a transdermal drug delivery system (DDS) and the rate of drug absorption (R_a) by the skin.

Basic components of TDS:

1) Polymer matrix or matrices
2) The drug
3) Permeation enhancers
4) Other excipients

Polymer matrix or matrices — controls the release of the drug from the device.

Criteria to be met by a polymer to be used in TDDS:

- Molecular weight, glass transition temperature and chemical functionality of the polymer should be such that the specific drug diffuses properly and gets released through it.
- Should be stable, non-reactive with the drug, easily manufactured and fabricated into the desired product; and inexpensive
- The polymer and its degradation products must be non-toxic and non antagonistic to the host.
- The mechanical properties of polymer should not deteriorate excessively when large amounts of active ahent are incorporated into it.

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.

The drug – Its desirable properties for transdermal delivery

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

Permeation enhancers - Classification

- **Solvents**

- Increase penetration possibly by swelling the polar pathway and/or by fluidizing lipids.
- e.g., water alcohols (methanol&ethanol), alkyl methyl sulfoxides (dimethyl sulfoxide, dimethyl acetamide,alkyl homologs of methyl sulfoxide), pyrrolidones (laurocapram, 2-pyrrolidone)

- **Surfactants**

- Enhance polar pathway transport, especially of hydrophilic drugs.
- These compounds being irritants, a balance between penetration enhancement and irritation has to be considered.
  Potential for irritation:- cationic > anionic > nonionic
  - **Anionic surfactants**:- Dioctyl sulfosuccinate, sodium lauryl sulphate
  - **Nonionic surfactants**:- Pluronic F127, Pluronic F68 etc.
  - **Bile salts**:- Sodium taurocholate, sodium deoxycholate

Permeation enhancers - Classification

- **Binary systems**

- These systems apparently open up the heterogenous multilaminate pathway aswell as the continate pathway.
- e.g., propylene glycol-oleic acid & 1,4-butane diol-linoleic acid

- **Miscellaneous chemicals**

- Hydrating and keratolytic agent
- N,N-dimethyl-m-toluamide
- Recently described:- eucalyptol, di-o-methyl-β-cyclodextrin

Other excipients - 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.

- Both type of adhesive systems should fulfill the following criteria
  - Should not irritate or sensitize the skin
  - Should adhere to skin aggressively during dosing interval without its position disturbed by activities such as bathing, exersise etc.
  - Should be easily removed
  - Should not leave an unwashable residue on the skin
  - Should hav excellent contact with the skin at macroscopic and microscopic level.

Other excipients - Adhesives

- **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:

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

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

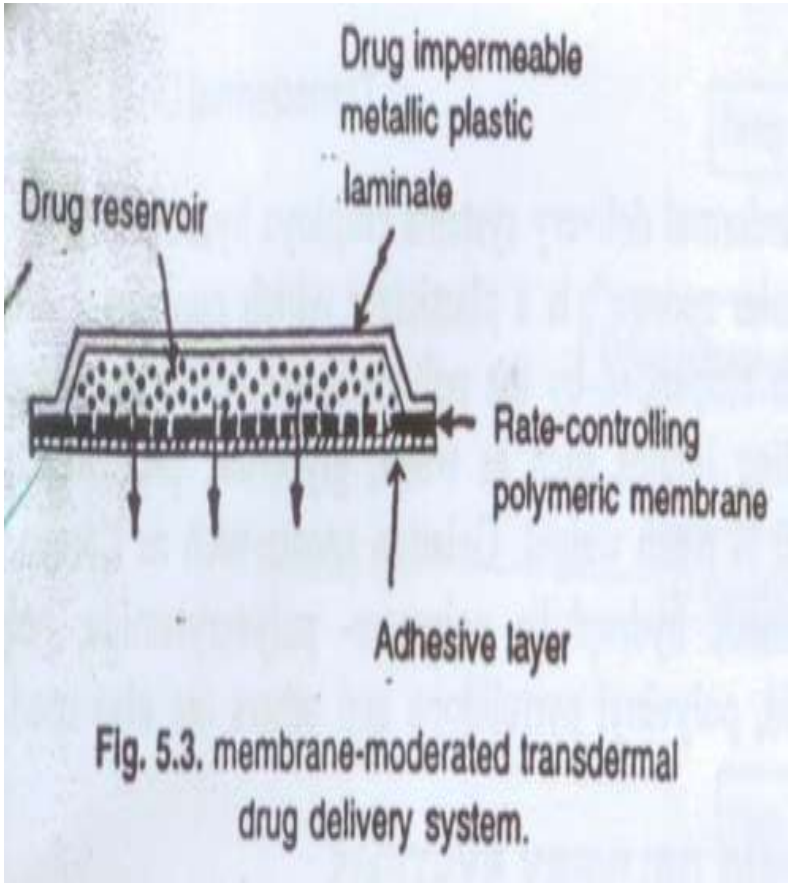

Fig. 5.3. membrane-moderated transdermal drug delivery system.

Membrane permeation – controlled systems

- Nitroglycerine – releasing transdermal system. For once a day medica in angina pectoris
- Scopalamine – releasing transdermal system for 72 hrs. Prophylaximotion sickness
- Clonidine – releasing transdermal system for 7 day therapy hypertension
- Estradiol – releasing transdermal system for treatment of menopausal syndrome for 3 -4 days.

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

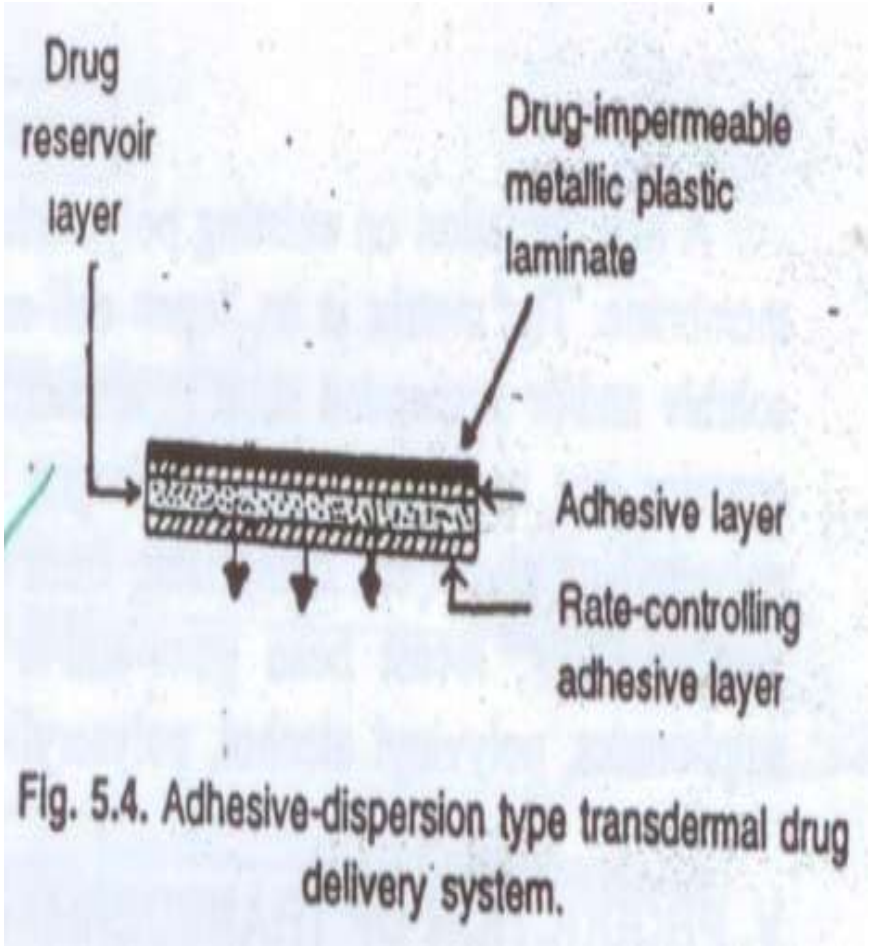

Fig. 5.4. Adhesive-dispersion type transdermal drug delivery system.

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:

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

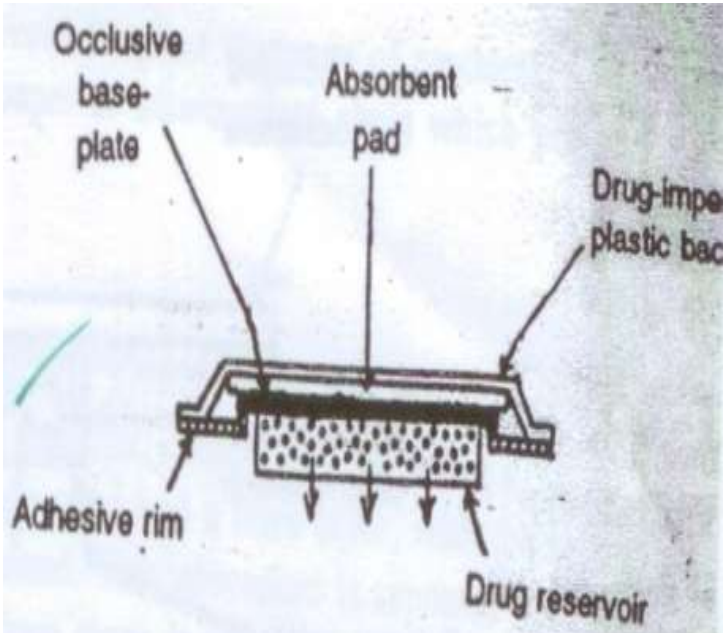

Fig. 5.6. Cross-sectional view of matrix diffusion co transdermal drug delivery system showing maj structural components.

Microreservoir type or microsealed dissolution controlled systems

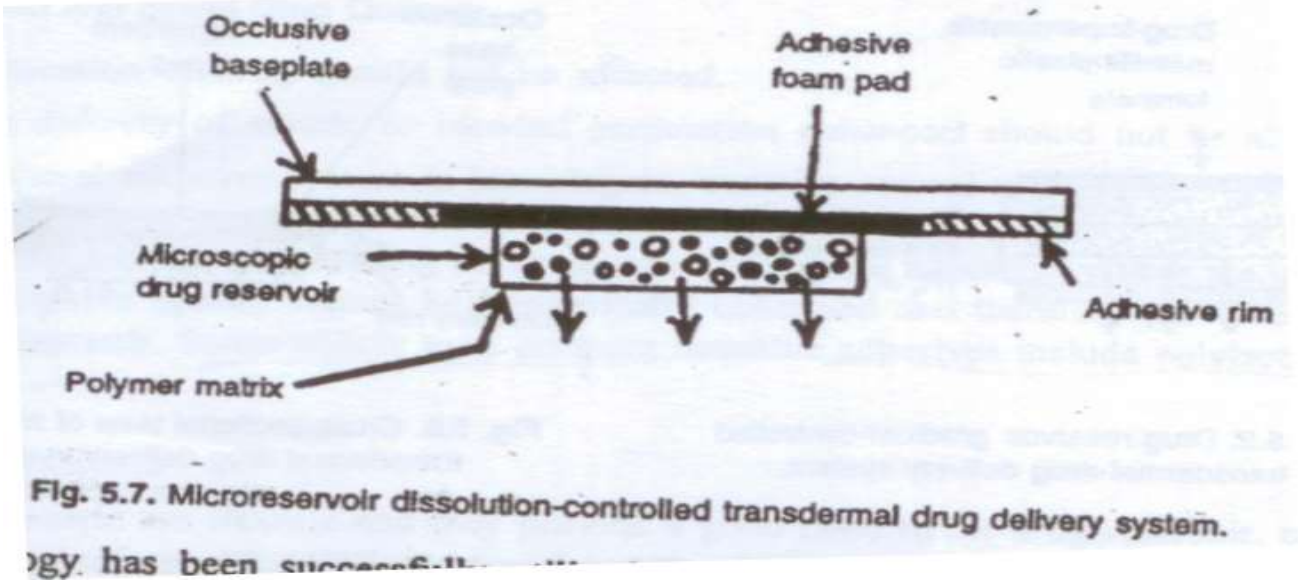

Fig. 5.7. Microreservoir dissolution-controlled transdermal drug delivery system.

ogy has been

- **Example:**

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

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"

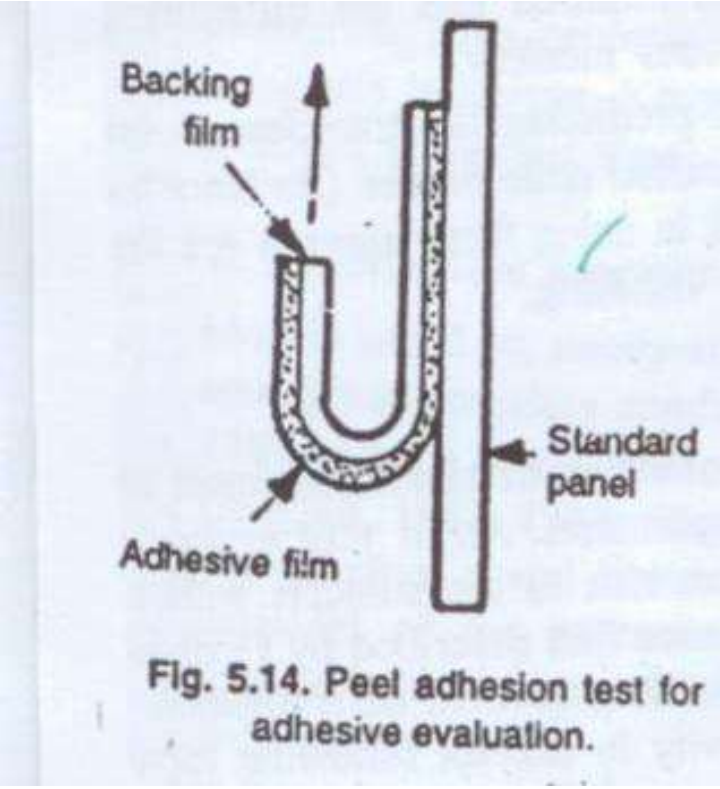

Fig. 5.14. Peel adhesion test for adhesive evaluation.

Evaluation of TDDS

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.

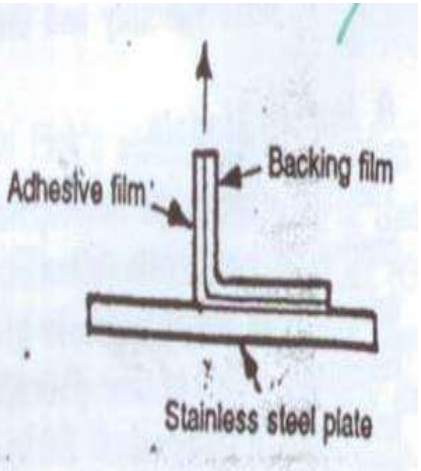

Fig. 5.16. Quick-stick (peel-tack) test for adhesive evaluation.

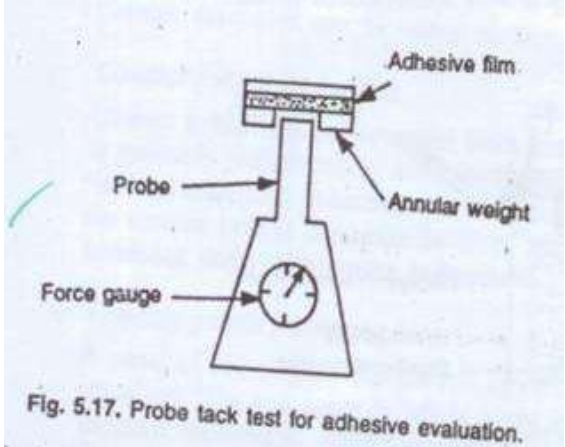

Fig. 5.17. Probe tack test for adhesive evaluation.

Evaluation of TDDS

c) Shear strength properties

- Measurement of the cohesive strenght of an adhesive polymer
- Affected by molecular weight, type & amount of tackifier added .
- The time taken to pull the adhesive coated tape off a stainless steel plate in a direction parallel to the plate, by a specific weight.

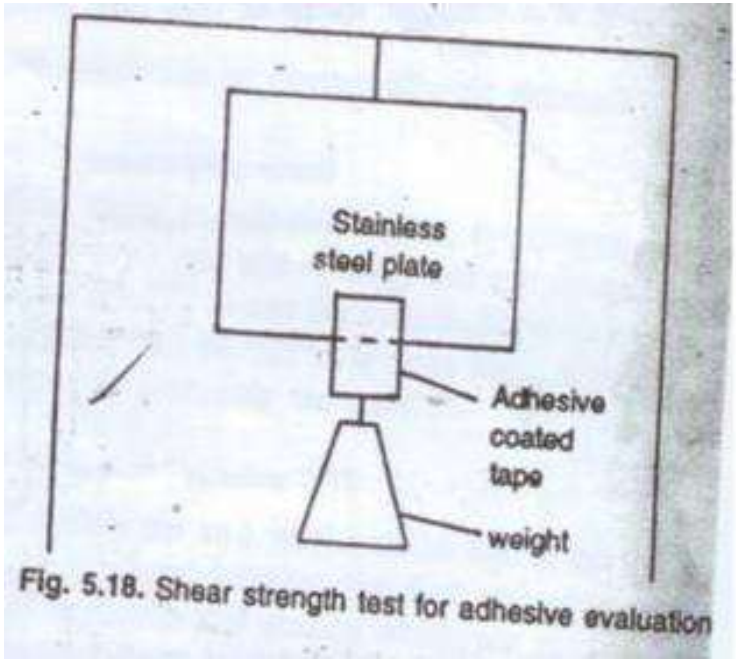

Fig. 5.18. Shear strength test for adhesive evaluation

Evaluation of TDDS

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

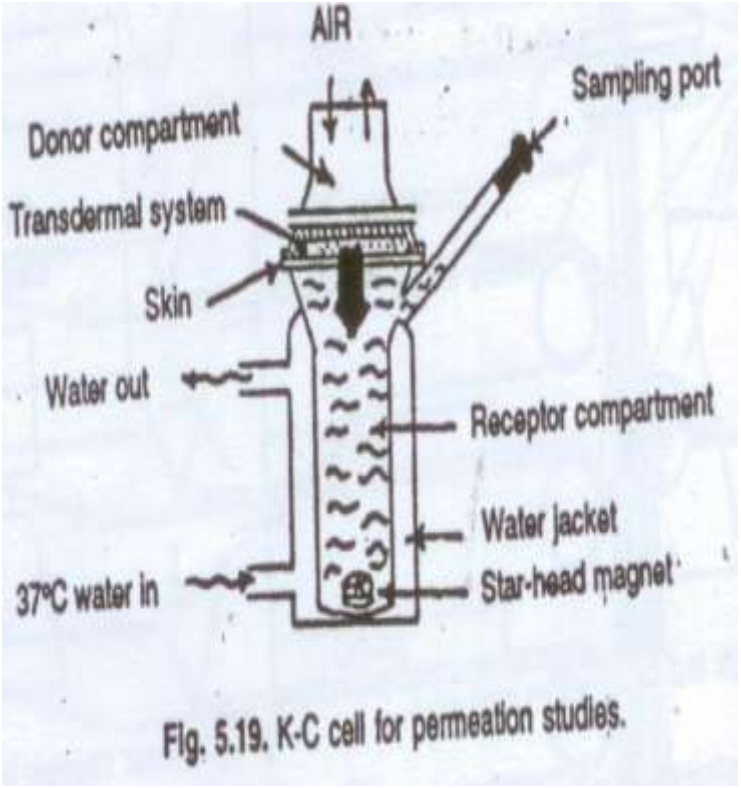

Fig. 5.19. K-C cell for permeation studies.

Evaluation of TDDS

2. **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

Evaluation of TDDS

2. **Invivo evaluation**

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

Evaluation of TDDS

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

THANK YOU