Transdermal Drug Delivery System

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DEFINITION

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

ADVANTAGES

- Avoid the risk and inconvenience of intravenous therapy
- Suitable in case of vomiting and diarrhoea
- Avoidance of first pass hepatic metabolism
- No gastrointestinal degradation
- Permit the continuous drug administration and the use of drugs with short biological half life.
- Extended therapy avoiding frequent dose administration
- Controlled drug delivery for a longer time

Cont…..

- **Bypasses the variation in absorption and metabolism associated with oral administration**
- **Reduces the chance of over and under dosing through the prolonged preprogrammed delivery of drug at the required therapeutic rate**
- **Better patient compliance**
- **Rapidly termination possible when needed simply by removing the patch from the skin surface**
- **Relatively large area (1-2m^2) of application in comparison with the buccal or nasal cavity**

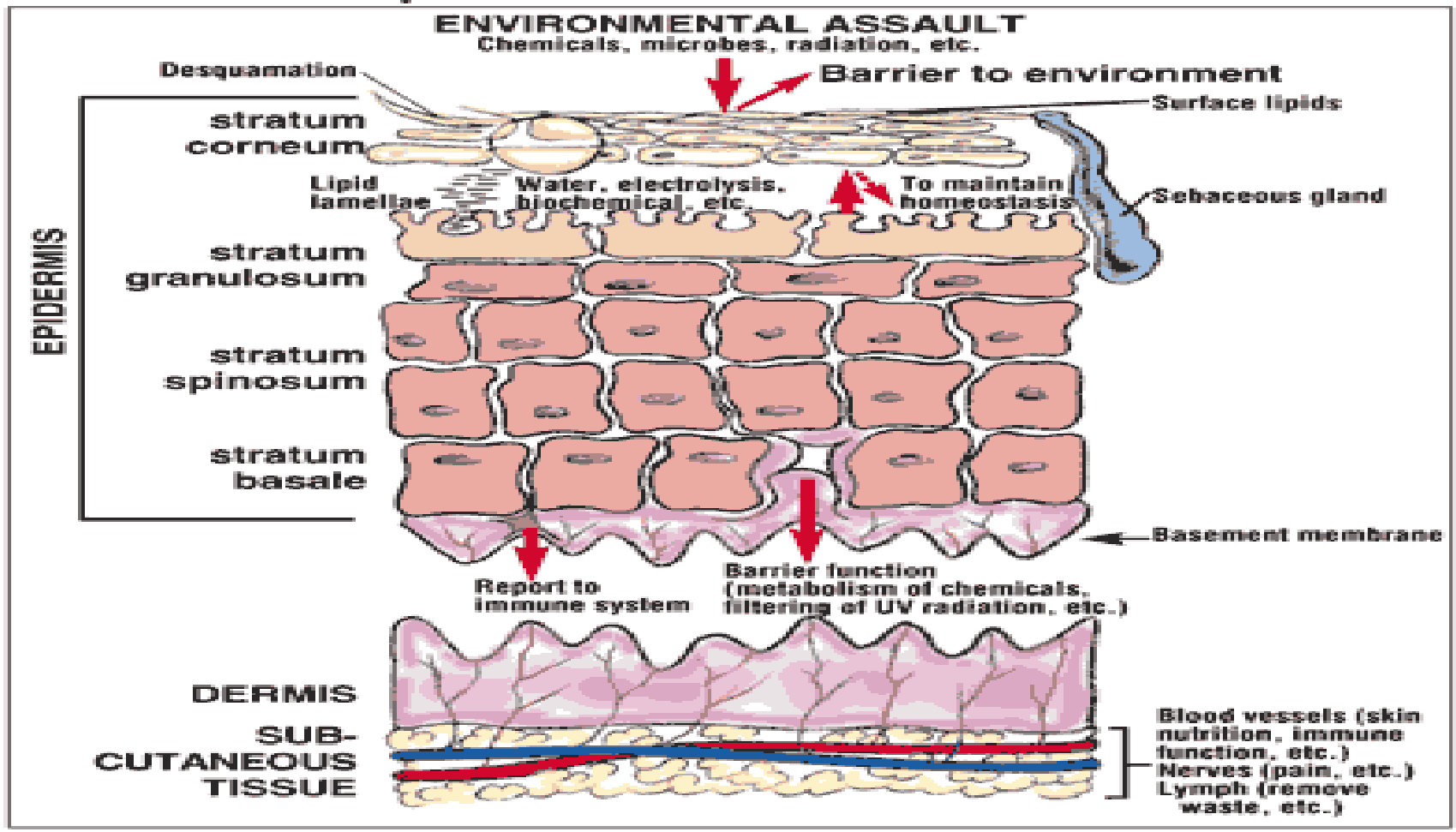
LIMITATIONS OF TDD

- Limited skin permeability
- Significant lag time
- Cannot be used for large molecule (>500 Dalton)
- Restricted to potent drug
- Skin irritation and allergic response
- Tolerance inducing drugs or those (e.g., hormones) requiring chronopharmacological management are not suitable candidates.

HUMAN SKIN

Figure 1

Skin Components and Functions Performed



ROUTES OF DRUG PENETRATION

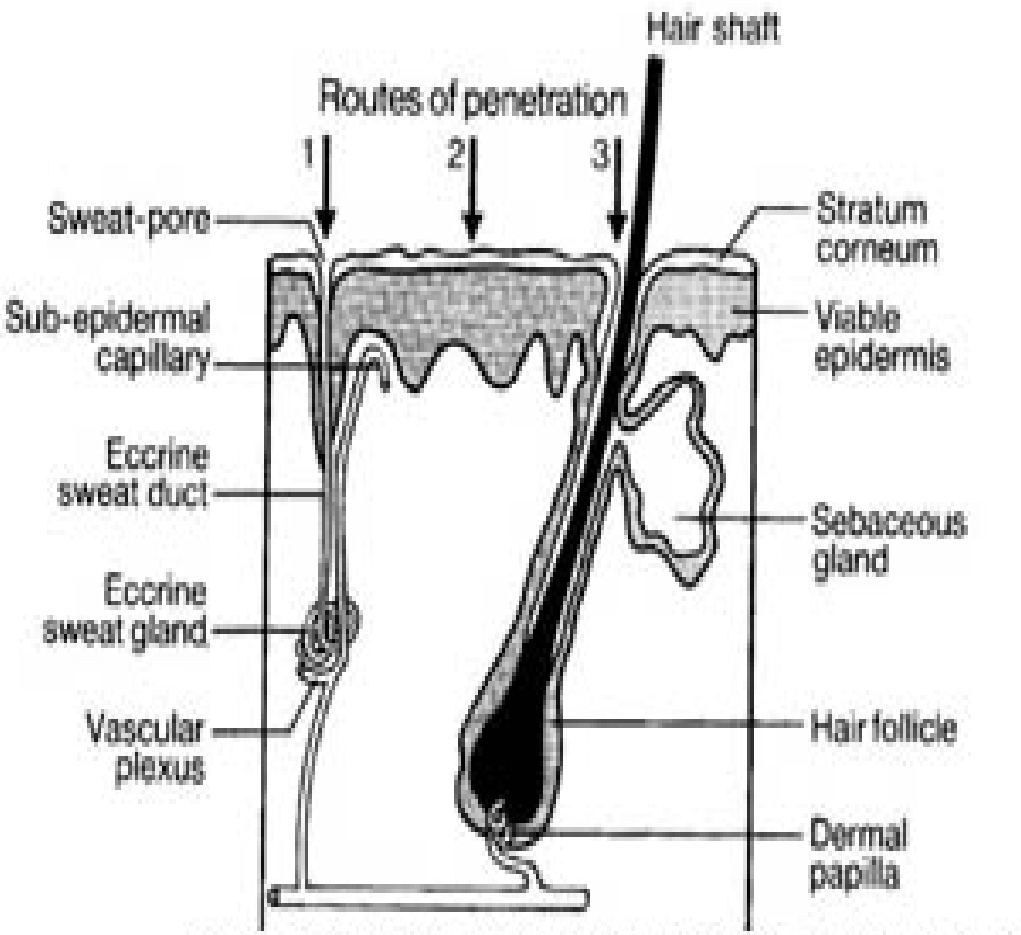
Macro routes

- SWEAT DUCT
- ACROSS STRATUM CORNEUM
- HAIR FOLLICLES

Micro routes

- INTERCELLULAR
- TRANSCELLULAR

MACRO ROUTES



Source: European Journal of Pharmaceutical Sciences 14 (2001) 101-114

1. **SWEAT DUCT**
2. **ACROSS STRATUM CORNEUM**
3. **HAIR FOLLICLES**

MICRO ROUTES

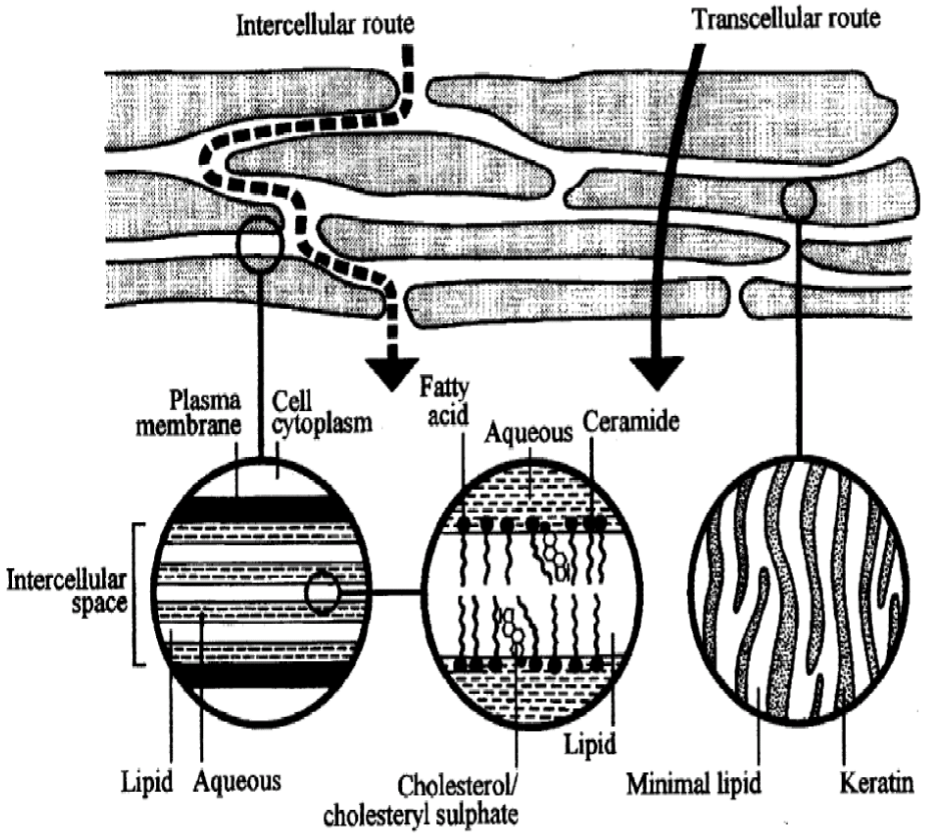


Fig. 2. Simplified diagram of stratum corneum and two microroutes of drug penetration.

1. **INTERCELLULAR**
2. **TRANSCELLULAR**

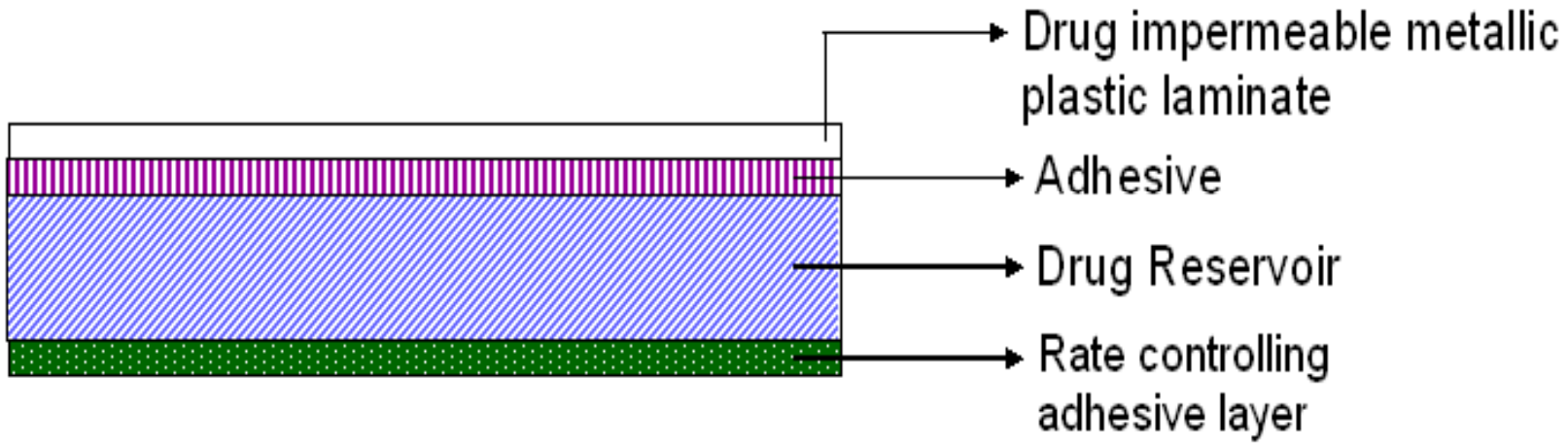
IDEAL DRUG CANDIDATE FOR TDD

1. Must be non-ionic
2. Low molecular weight (less than 500 Daltons)
3. Lipophilicity
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.

CLASSIFICATION OF TDDS

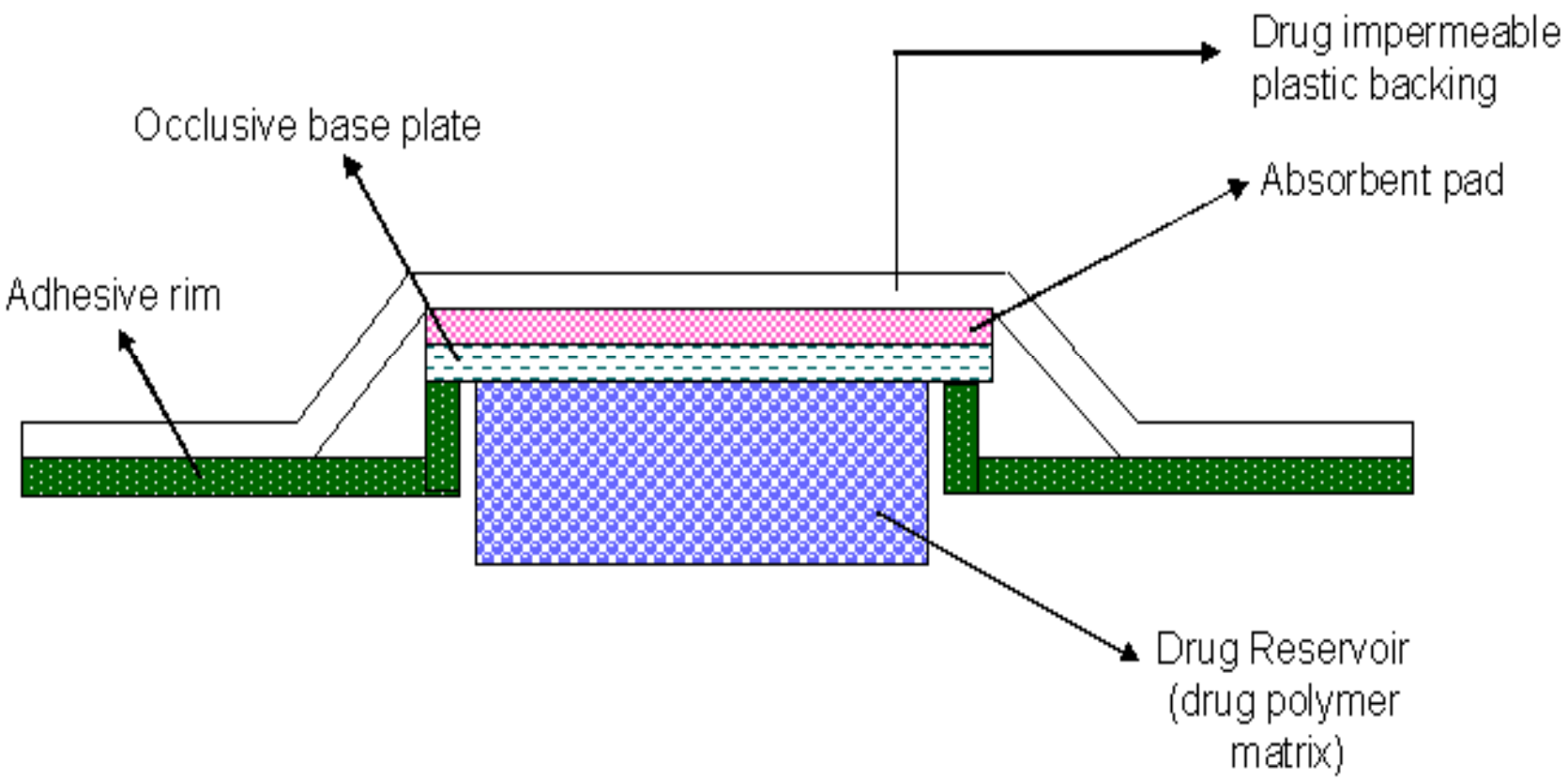
- **MATRIX SYSTEM --- DRUG IN ADHESIVE SYSTEM (ADHESIVE DIFFUSION CONTROLLED TDDS)**
- **MATRIX SYSTEM --- MATRIX DISPERSION SYSTEM (MATRIX DIFFUSION CONTROLLED SYSTEM)**
- **RESERVOIR SYSTEM (MEMBRANE MODERATED TDDS)**
- **MICRORESERVOIR SYSTEM**

MATRIX SYSTEM --- DRUG IN ADHESIVE SYSTEM (ADHESIVE DIFFUSION CONTROLLED TDDS)



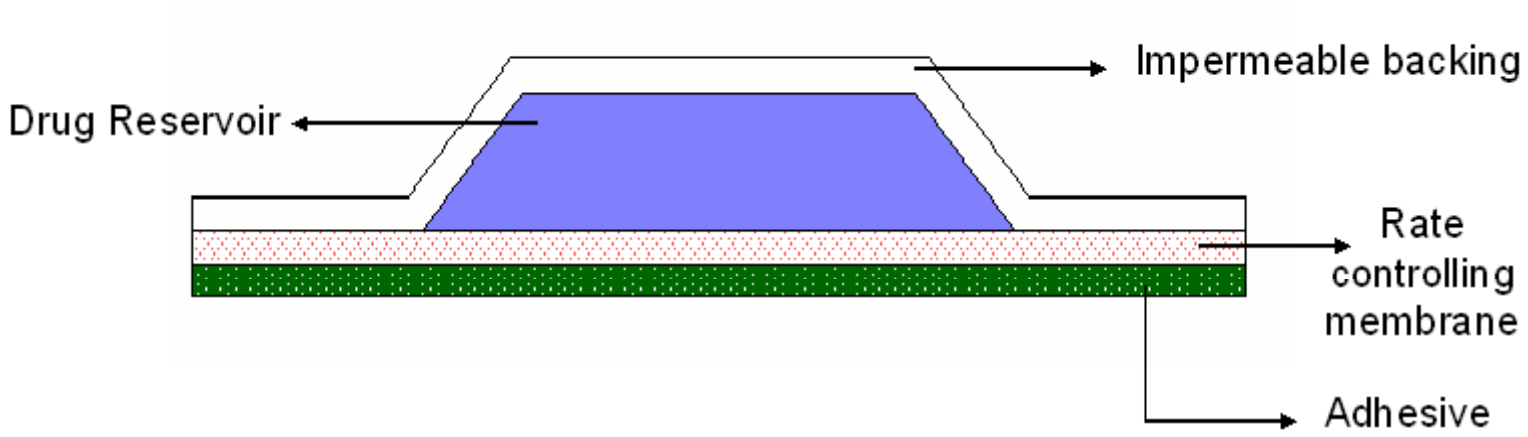
Deponit® (Nitroglycerine) for once a day for angina pectoris.

MATRIX SYSTEM --- MATRIX DISPERSION SYSTEM (MATRIX DIFFUSION CONTROLLED SYSTEM)



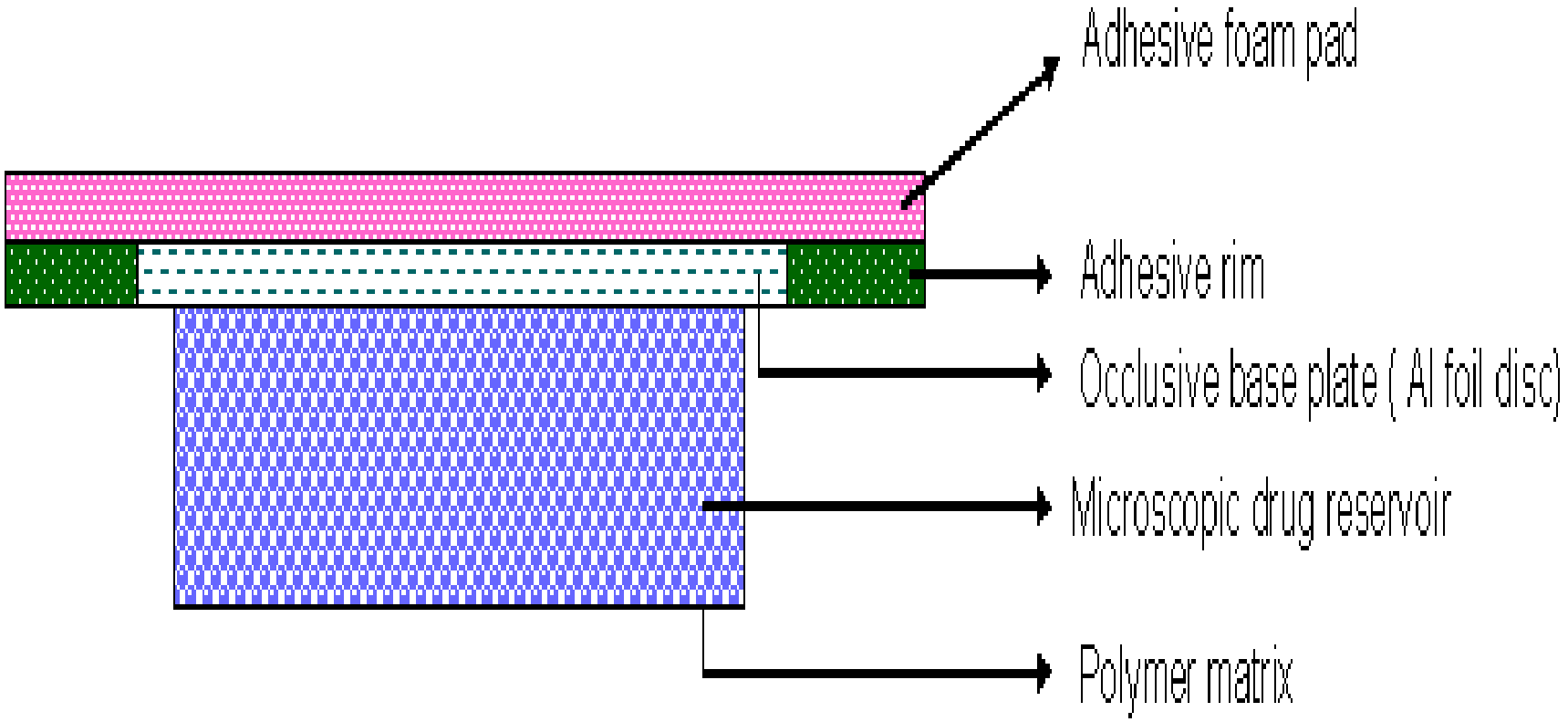
Nitro Dur® **(Nitroglycerine) used for once a day for angina pectoris.**

RESERVOIR SYSTEM (MEMBRANE MODERATED TDDS)



TransdermScop® (Scopolamine) for 3 days protection of motion sickness

MICRORESERVOIR SYSTEM



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

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

BACKING FILMS

ROLE OF FILM :

1. To protect the active layer and safeguard the stability of the system,
2. To affect skin permeation and tolerance, depending on occlusion or breathability.
3. It must also be flexible, comfortable and must present good affinity with the adhesive, as well as excellent printability.

MOST COMMON MATERIALS USED :

- polypropylene,
- polyethylene (both high and low density),
- saran,
- polyesters, PVC,and nylon.

RELEASE LINERS

ROLE OF FILM :

1. To protect the system as long as it is in the package.
2. Play a crucial role in the stability of the product .
3. An incorrect release liner does not permit the easy release of the patch, and can interfere with the active(s) or other components, thereby reducing its shelf life.

Cont...

MOST COMMON FILMS USED :

- ⇨ **paper-based,**
- ⇨ **plastic film-based and**
- ⇨ **composite films.**

- **TWO MAJOR CLASSES OF ANTI-ADHERENT COATING :**

- ⇨ **silicones and**
- ⇨ **fluoro-polymers.**

PRESSURE-SENSITIVE ADHESIVES

- **CORRECT CHOICE OF PSA :**

  1. **A critical effect on the stability of the system,**
  2. **Release of the active,**
  3. **Dermatotoxicity potential,**
  4. **Accurate administration of the drug.**

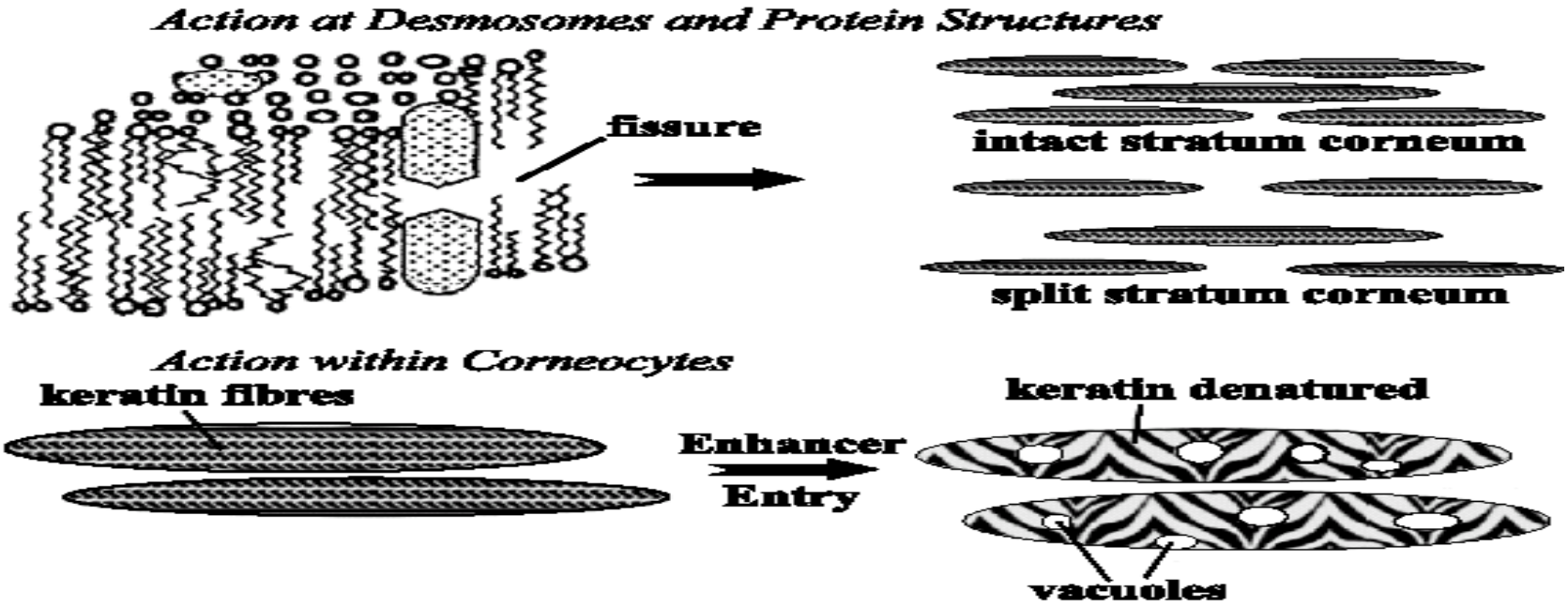
- **THREE MAJOR FAMILIES OF PSAS:**

  1. **Rubber-based PSAs,**
  2. **Acrylic PSAs in the form of acrylic solutions,**
  3. **Emulsion polymers or hot melts, and silicon PSAs**

(E) PERMEATION ENHANCERS

THREE POSSIBLE MECHANISM :

1. Lipid Action
2. Protein Modification
3. Partitioning Promotion



CHEMICAL CLASS	EXAMPLE(s)
Fatty acids	Oleic acid, Undecanoid acid
Fatty alcohols	Octanol, Nonanol
Terpenes	Menthol, Thymol, Limonene
Sulfoxides	Dimethyl sulfoxide, Dodecyl methyl sulfoxide
Anionic surfactants	Sodium lauryl sulfate
Cationic surfactants	N,N-bis (2 hydroxy ethyl) oleylamine
Nonionic surfactants	Polyoxyethylene(20) sorbitan mono oleate
Zwitterionic surfactants	Dodecyl dimethyl ammoniopropane sulfate
Polyols	Propylene glycol, Polyethylene glycol
Amides	n,n-dimethyl-m-toluamide
Ureas	Urea
Lactam	Laurocaparan (Azone®)
Sugars	Cyclodextrins

(G) MICROPOROUS OR SEMI-PERMEABLE MEMBRANES

ROLE OF THE MEMBRANES

- To limit the flow of the semi-solid content from the liquid reservoir, and/or to act as a rate-limiting membrane for both liquid reservoir and matrix systems.

TWO TYPES OF POROUS MEMBRANES

I Ethylene Vinyl Acetate Membranes (EVA)

II Microporous Polyethylene Membranes

(H) POUCHING MATERIALS

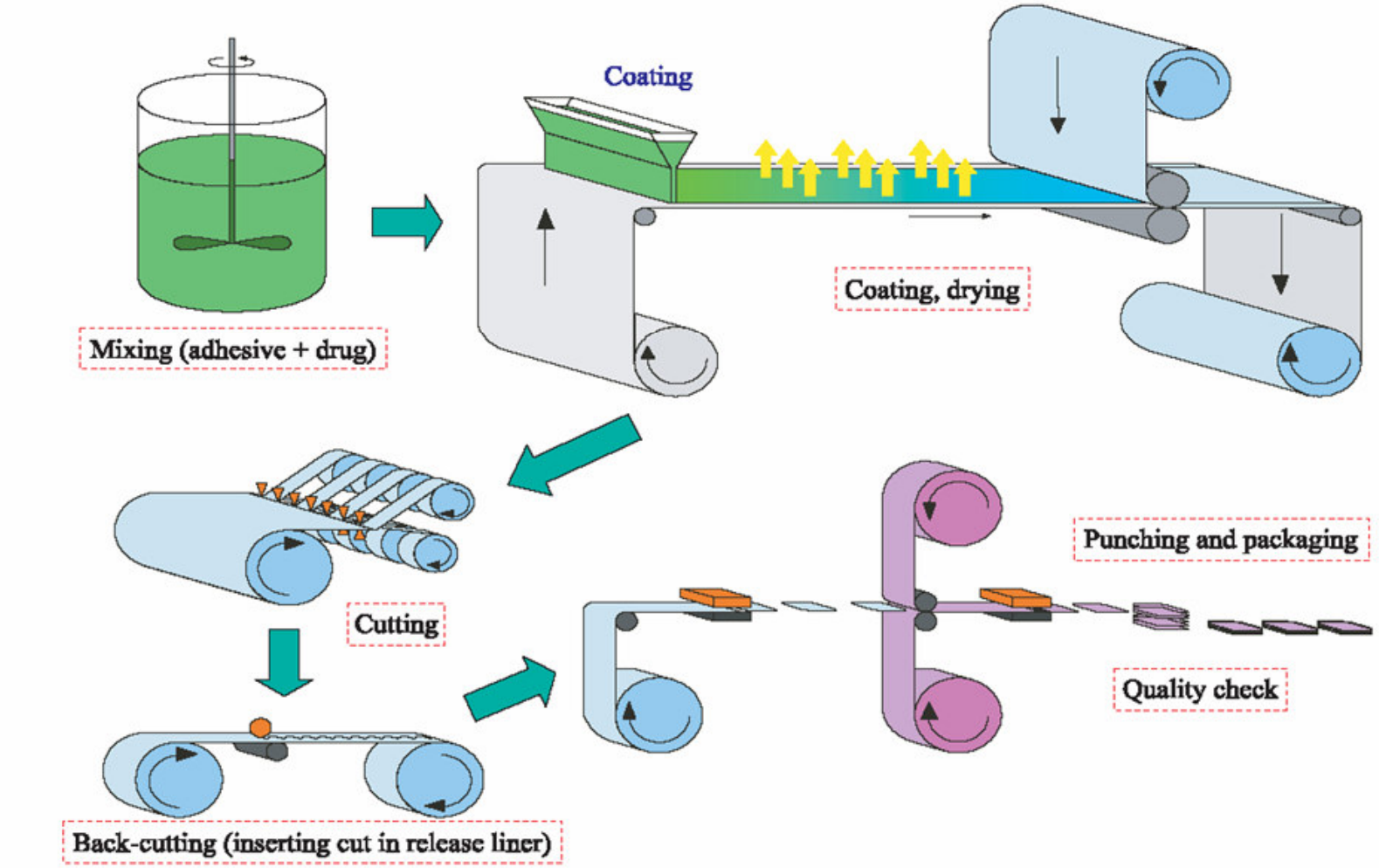
- **ROLE :**

  1. Stability and integrity of the product

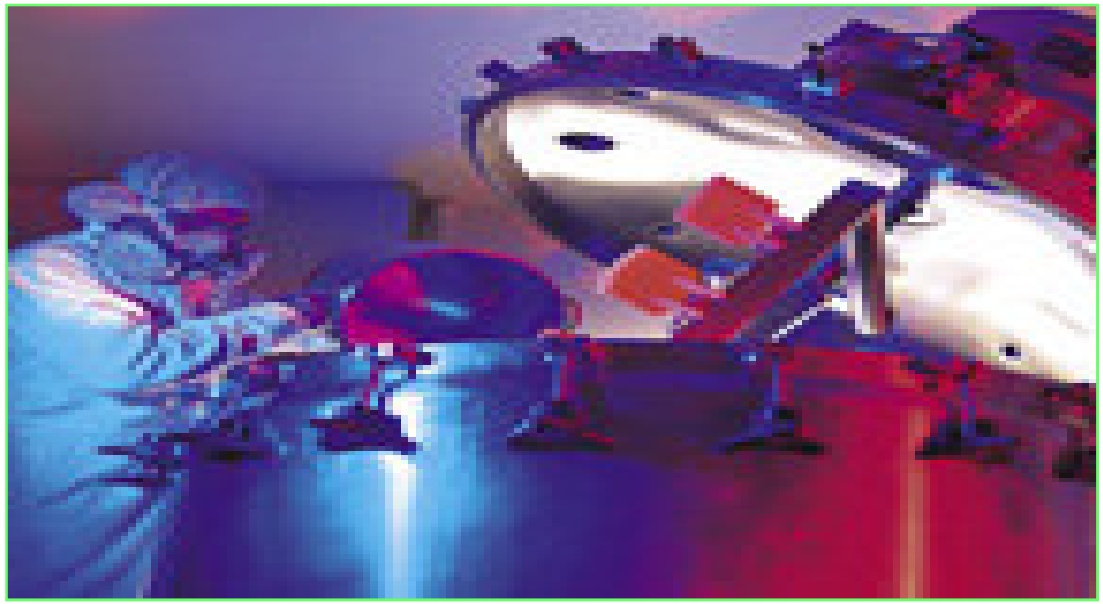
- **THREE MAIN LAYERS IN THE COMPOSITE MATERIALS USED FOR POUCHES:**

  1. **Internal plastic heat sealable layer,**
  2. **Aluminium foil layer**
  3. **External printable layer.**

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

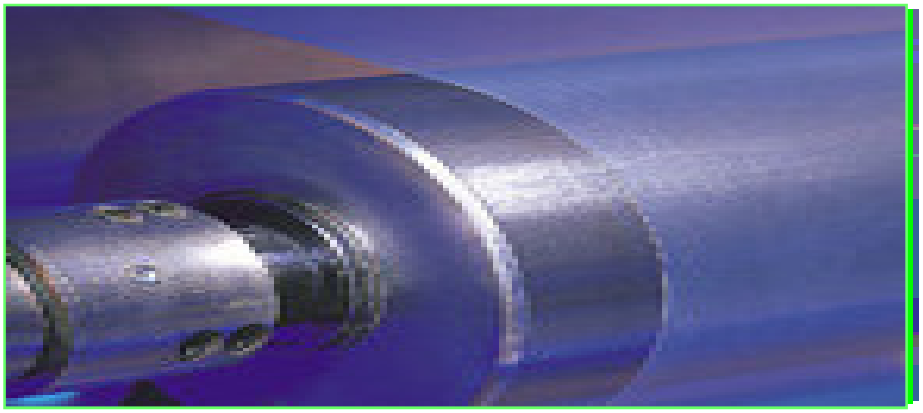


1. BLENDING



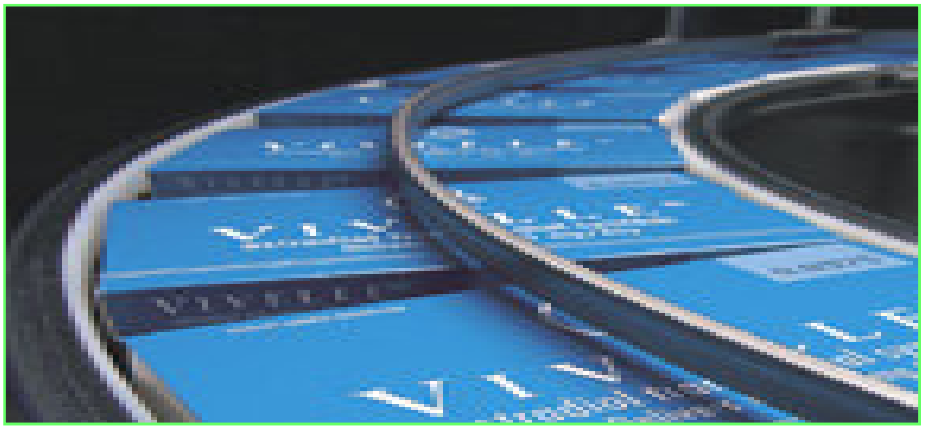
2. COATING

3. COMPLETED LAMINATE IS THEN ROLLED



4. PUNCHING

5. POUCHING AND CARTONING

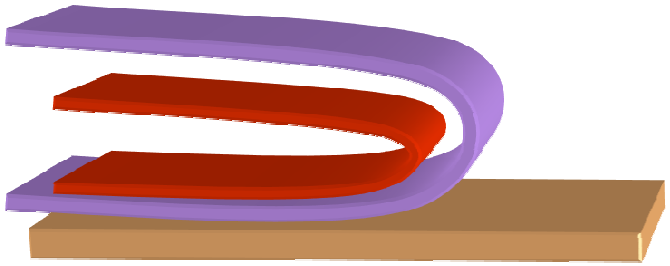


EVALUATION OF TDDS

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 Sensitization study
PERCUTANEOUS ABSORPTION MODEL	In vitro testing In vivo testing Human IVIVC

ADHESION TEST

1 PEEL ADHESION TEST



BACKING LAYER

ADHESIVE LAYER

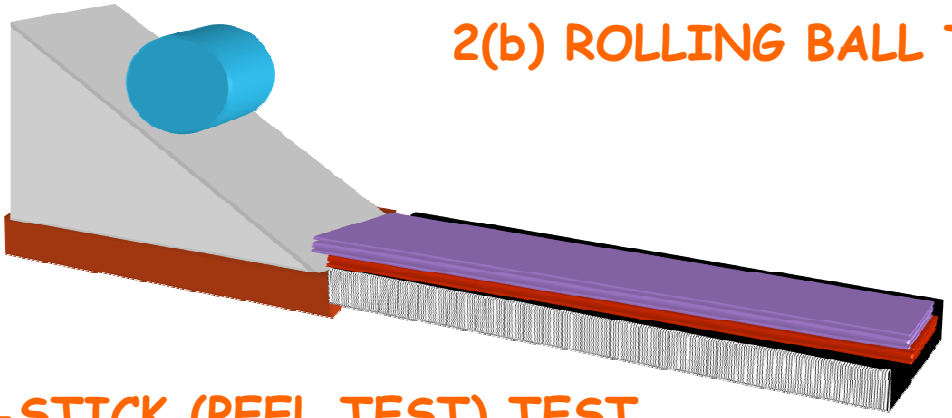
- **The force required to remove an adhesive coating from a test substrate is referred to as peel adhesion.**
- **The force is expressed in ounces (or grams) per inch width of tape.**
- **If higher value then it indicates greater bond strength.**

2. TACK PROPERTY :

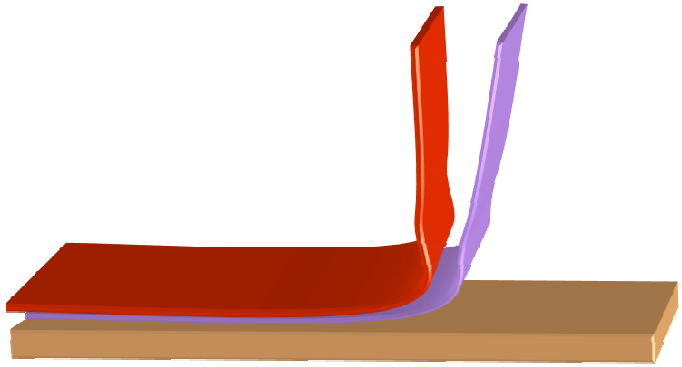
2(a) THUMB TACK TEST

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

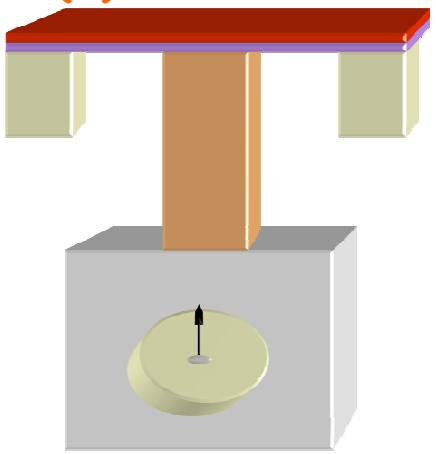
2(b) ROLLING BALL TACK TEST



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

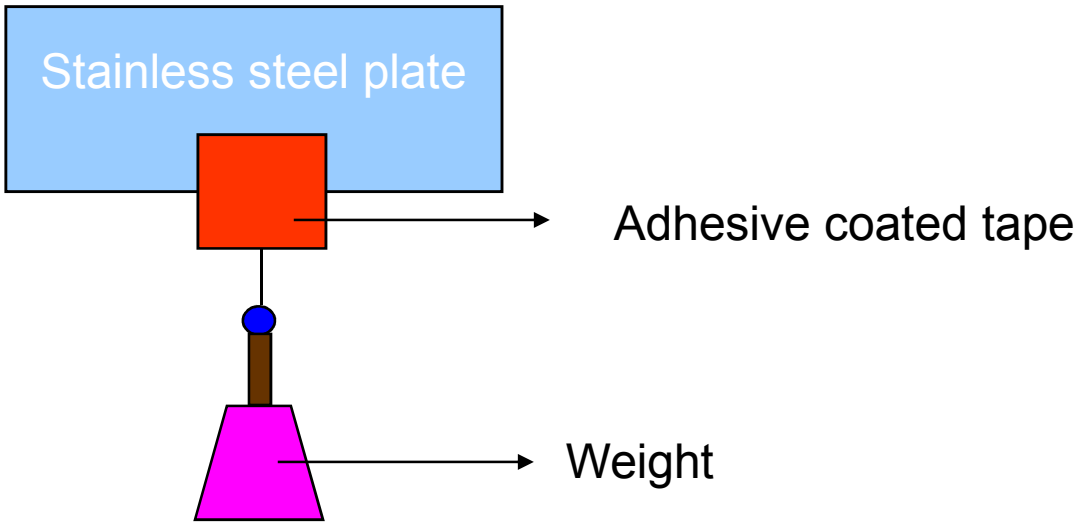


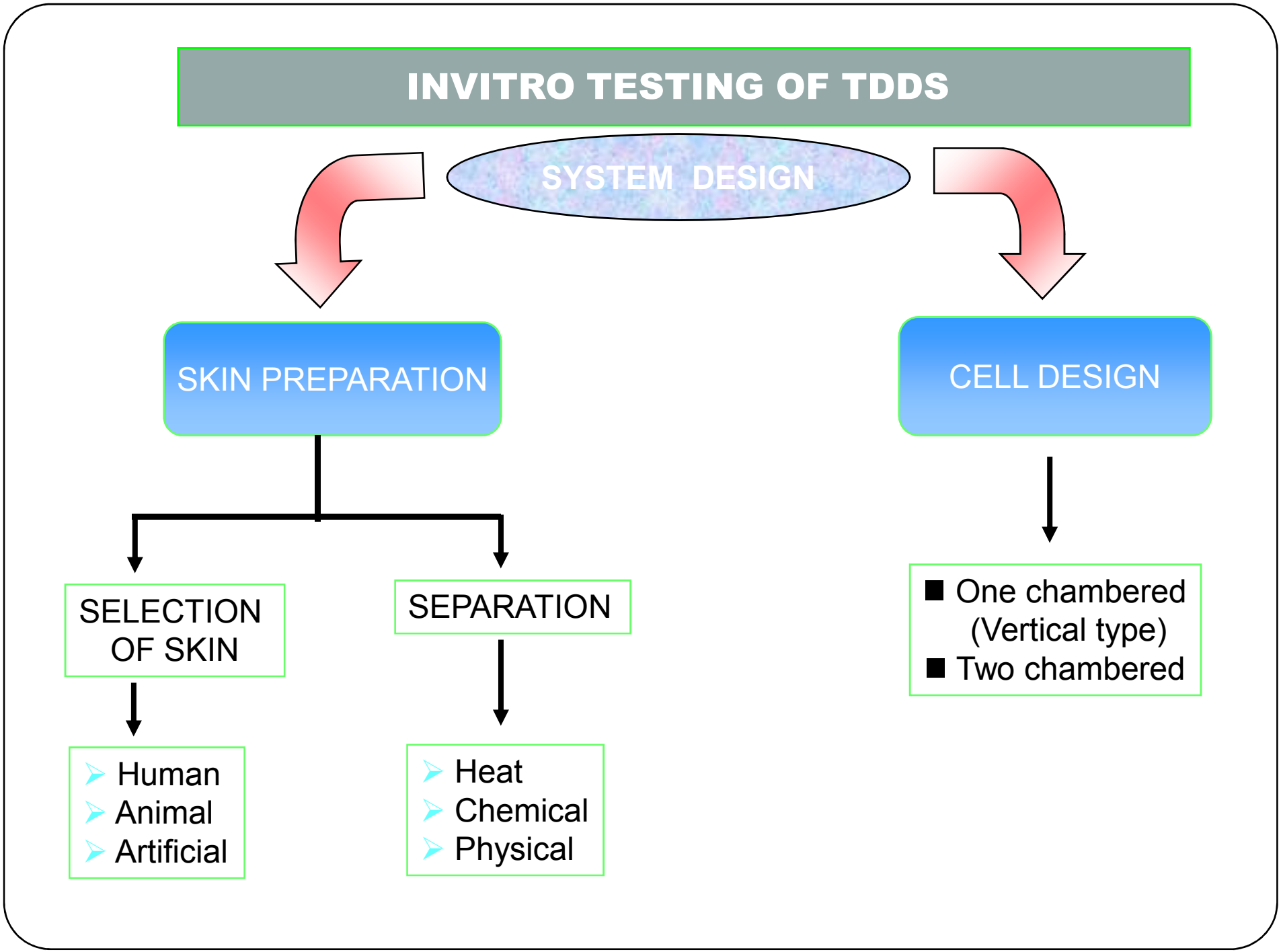
2(d) PROBE TACK TEST



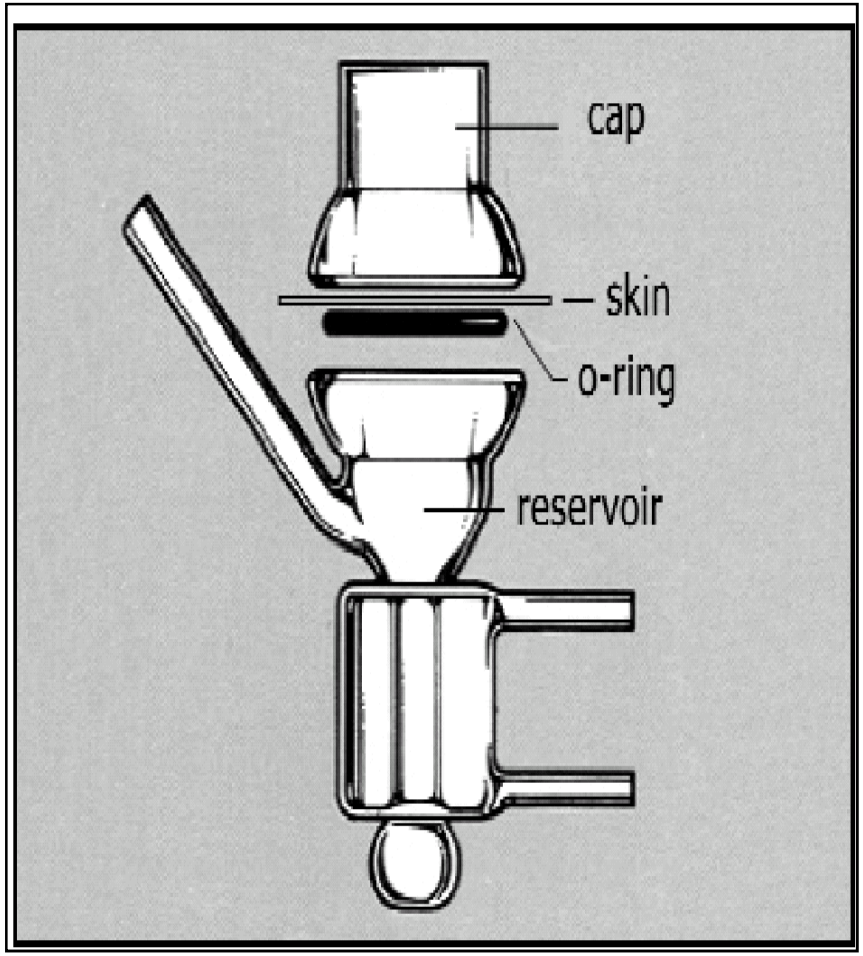
- **Polyken probe tester**
- **The tip of clean probe is brought into contact with adhesive, and when a bond is formed between probe and adhesive. The force required to pull the probe away from the adhesive at fixed rate is recorded as tack (Grams).**

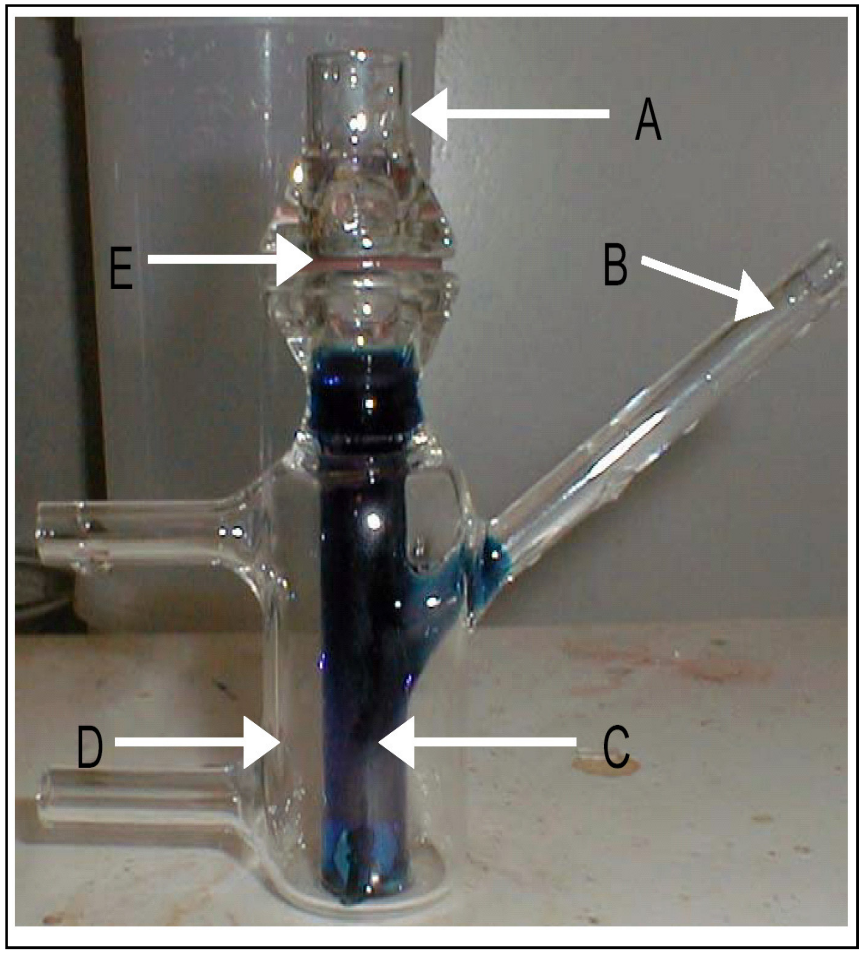
3 SHEAR STRENGTH TEST




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

DESIGN OF FRANZ DIFFUSION CELL



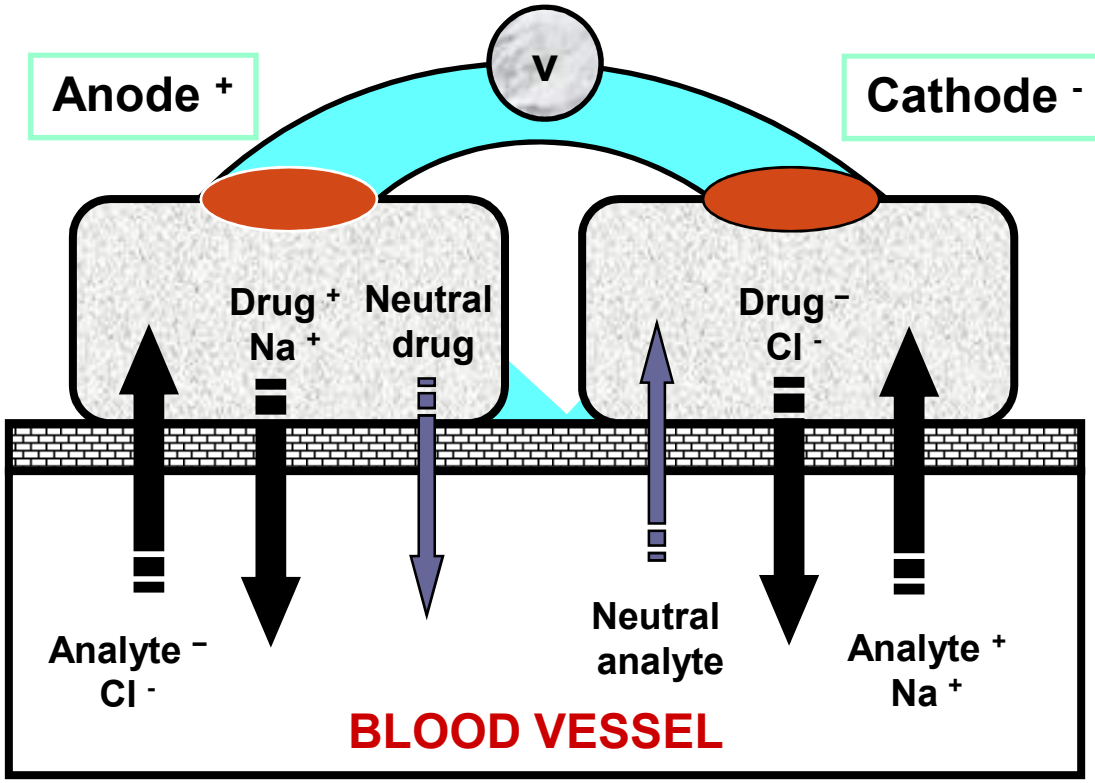


INNOVATIONS TRANSDERMAL DRUG DELIVERY

IONTOPHORESIS

- facilitated penetration of ions into surface tissues such as skin, oral mucosa and other epithelia under an externally applied potential difference.
- It involves the application of small electric current (usually 0.5 mA/cm^2) to drug reservoir with the same charged electrode.
- Electrorepulsion effect drives the solute into the skin.
- The possibility of increasing the stratum corneum permeability in the presence of a flow of an electric current.

ELECTROCHEMISTRY OF IONTOPHORETIC CIRCUIT [ELECTROREPULSION]



The number of electrons flowing through the external circuit is a direct reflection of the amount of ionic charges flowing through the skin.

The transport number and the intensity of current are the two main parameters controlling the iontophoretic flux.

IDEAL DRUG CANDIDATE FOR IONTOPHORESIS

Aqueous Solubility **: > 1 mg/ml**

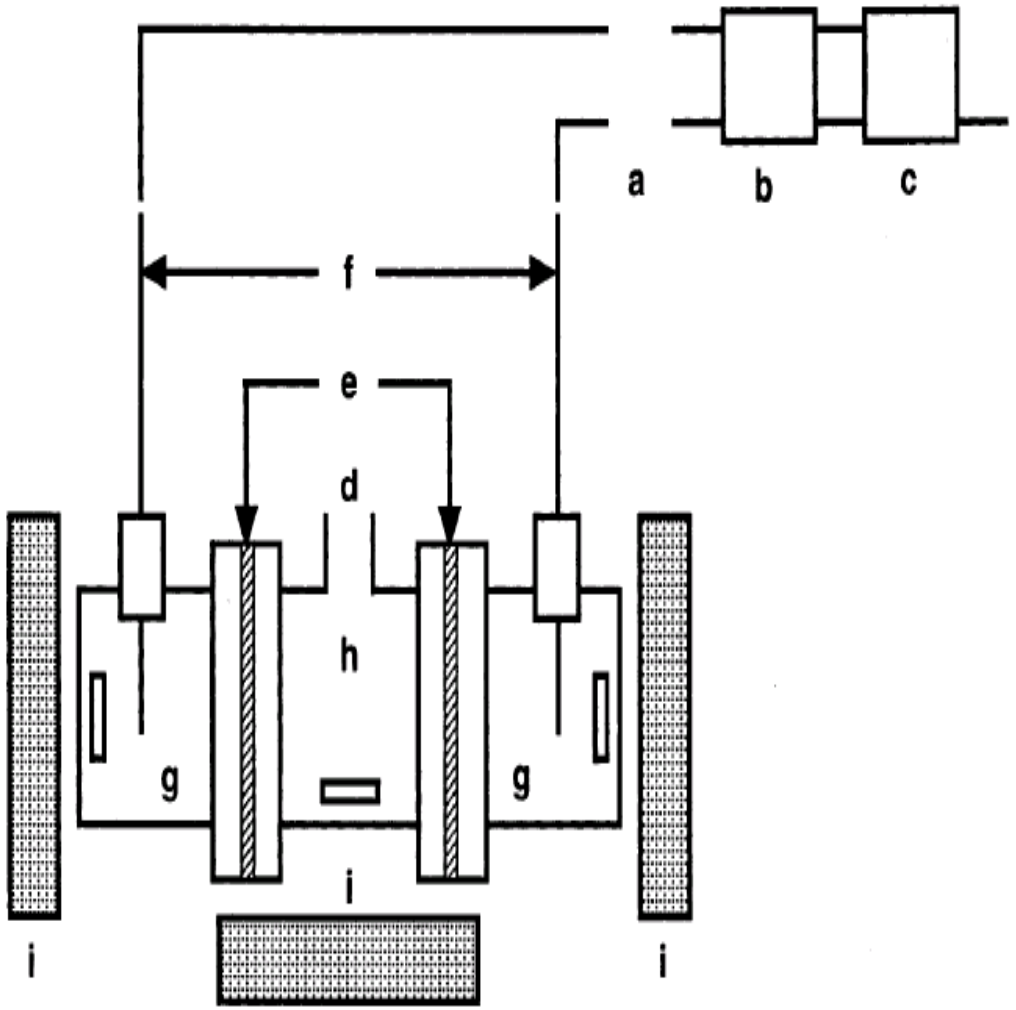
Charge **: pK_a or pI < 4 (for acids)**
> 7.4 (for bases)

Dose Deliverable **: 20 – 50 mg/day for MWt < 1000 Da**
2 – 5 mg/day for 1000Da<MWt<5000 Da
< 1 mg/day for MWt > 5000 Da

pKa – Ionization constant and pI – Isoelectric point

SWITCHING IONTOPHORESIS (PULSED CURRENT)

Applied voltage is switched at regular interval
No accumulation of H^+ ions
Hydration of SC is much more higher as compared to simple iontophoresis. So drug flux is comparatively higher
Reduce skin irritation even after prolong period of application. So current voltage can be increased
Reusable. So total cost of therapy decreases

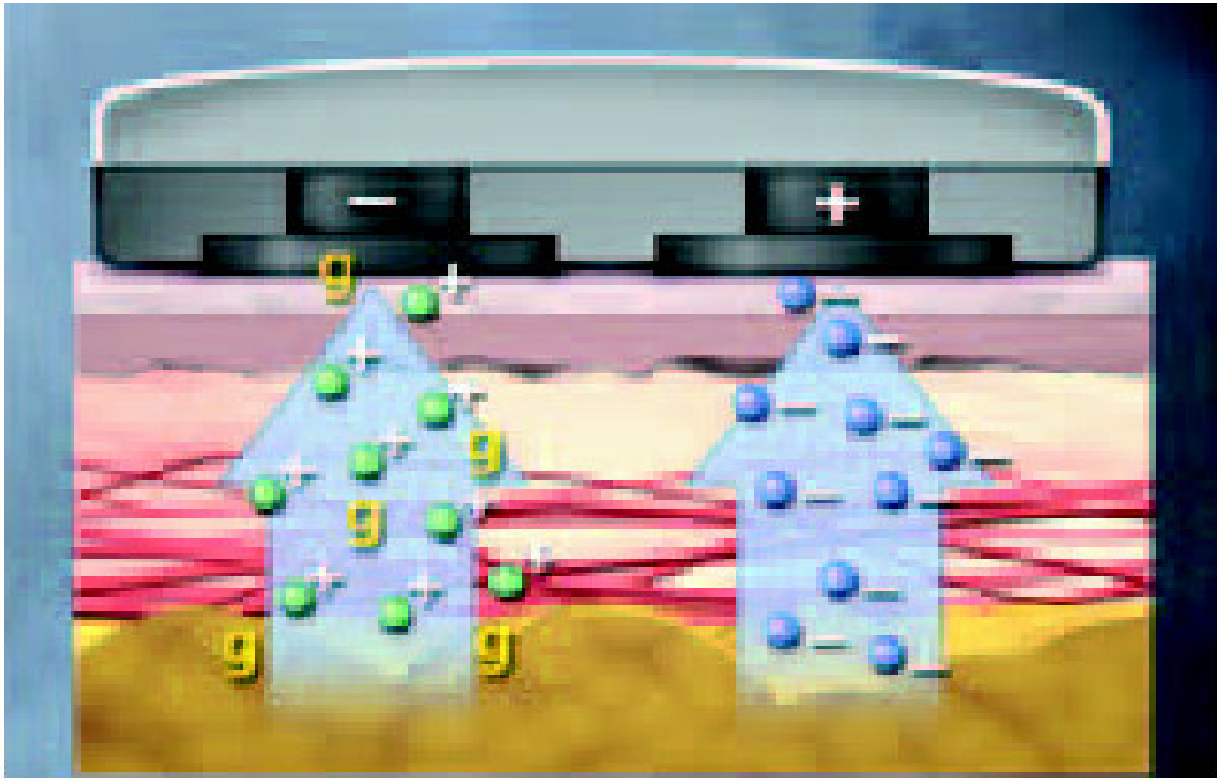


a. Switch
b. Amplifier
c. Oscillator
d. Sampling Port
e. Skin (3.53 cm2)
f. Electrodes
g. Donor (2.65 ml)
h. Receiver (6.00 ml)
i. Magnetic stirrer

REVERSE IONTOPHORESIS

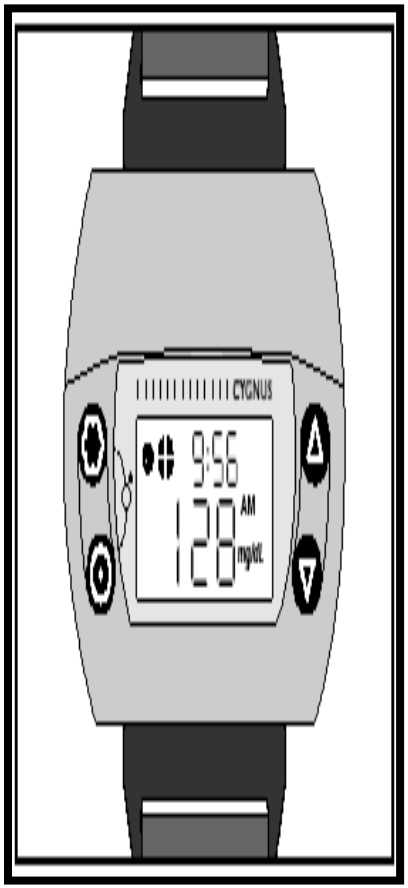
- Symmetrical nature of iontophoresis has led to its application as a noninvasive method of extracting endogenous substances known as REVERSE IONTOPHORESIS
- Potential tool for therapeutic monitoring
- Suggested for noninvasive monitoring of phenylalanine levels (phenylketonuria)
- GLUCOWATCH BIOGRAPHER® approved by FDA in 2001

GLUCOWATCH BIOGRAPHER®



Glucose molecules being pulled through the skin

g = glucose molecules
− = negative ion
+ = positive ion



ADVANTAGES OF IONTOPHORETIC DD

Iontophoresis enlarges the range of drug candidates for transdermal administration
Fast skin recovery
Minor irritation
Less sensitive to the condition of the skin at the application site

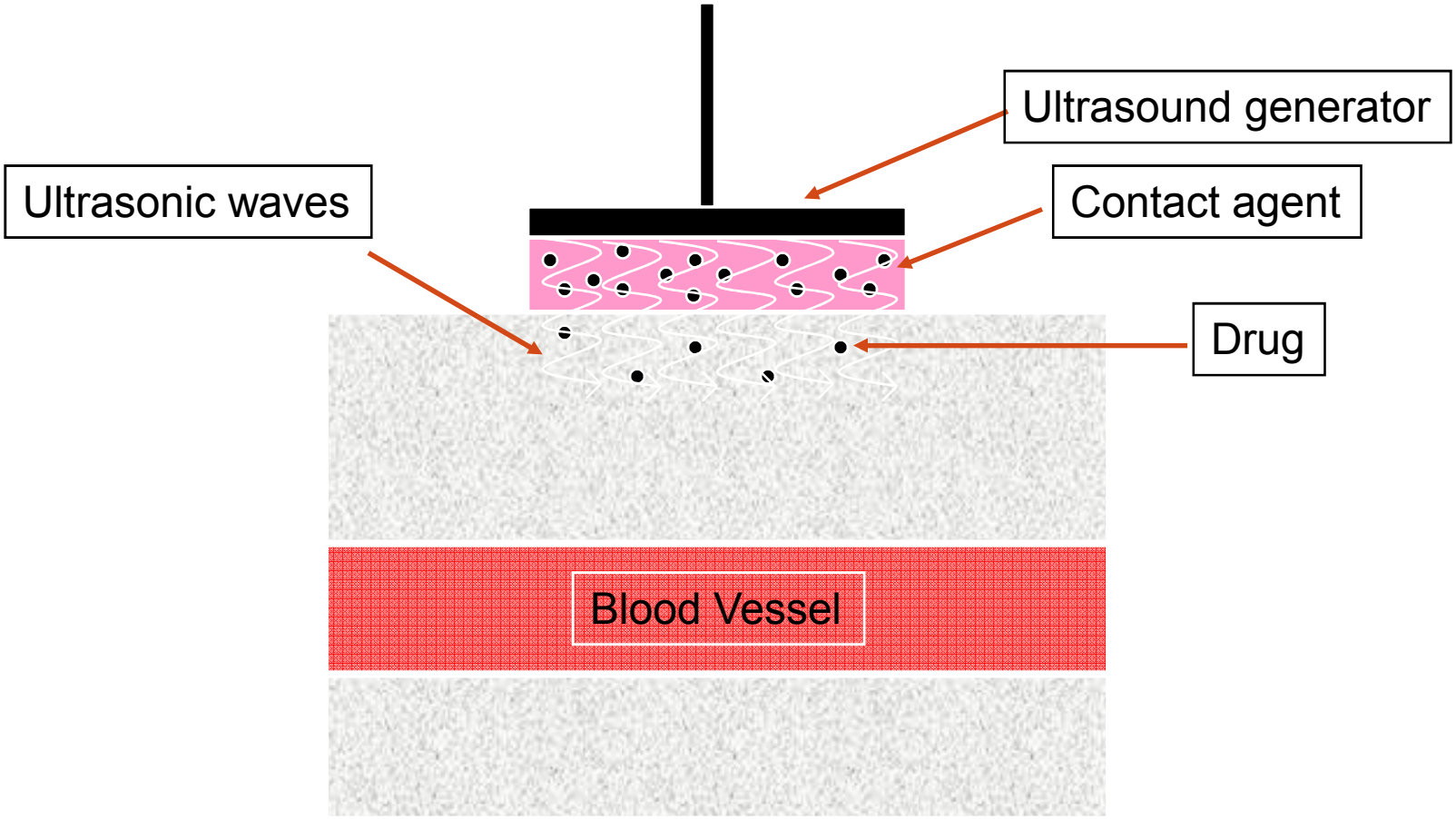
DISEASE CATEGORY		DRUG DELIVERED BY IONTOPHORETIC DRUG DELIVERY
Pain managing	Opiods	Morphine. Meperidine, Fentanyle, Buprenorphine
	NASIDS	Piroxicam, Diclofenac, Nalbuphine, Ketorelac, Ketoprofen,
	Local anesthetics	Lidocaine
	Migraine	Alniditan
Neurodegenerative condition		B-Apomorphine, Ropinirole, Tacrine
Skin cancer		Cisplatin, Vinblastine, Methotrexate, Khellin, 5FU, ALA
Antiemetics		Metaclopramide, Domperide,
Antiviral		AZT, Acyclovir
CVS		Propranolol, Isoprenaline, Timolol, Arbutamine, Verapamil
Steroid		Prednisolone, Dexamethasone
Protein & Peptides		Insulin, Calcitonin, HPTH, LHRH and its analogues, Somatostatin, Somatotropin

ULTRASOUND / SONOPHORESIS / PHONOPHORESIS

- migration of the drug molecules, contained in a coupling contact agent, through intact skin into soft tissue under the influence of ultrasonic perturbations.

- Applied frequency range from 20 KHz – 16 MHz

TYPE	FREQUENCY	MECHANISM	DRUG
Low frequency sonophoresis	***20 KHz - 1 MHz***	• ***Cavitational*** • ***Formation of aqueous channel into lipid of SC***	• ***Hydrophilic drug*** • ***Protein***
Moderate frequency sonophoresis (Therapeutic ultrasound)	***1 - 3 MHz***	• ***Structural disorder of SC in lipid due to collapse of cavitational bubble***	• ***Corticosteroid*** • ***Dexamathasone*** • ***Estradiol*** • ***Hydrocortisone*** • ***Progesterone***
High frequency Sonophoresis	***3 MHz - 16MHz***	• ***Enhance skin permeation due to oscillation of bubble***	• ***Salicylic acid*** • ***Lanthanum tracers***



SONOPHORETIC DELIVERY

Drug penetration enhancement may be by : thermal, mechanical, and/or chemical effects

ELECTROPORATION

Application of large transmembrane voltages (100V) caused by electrical pulses (10μs – 100ms)

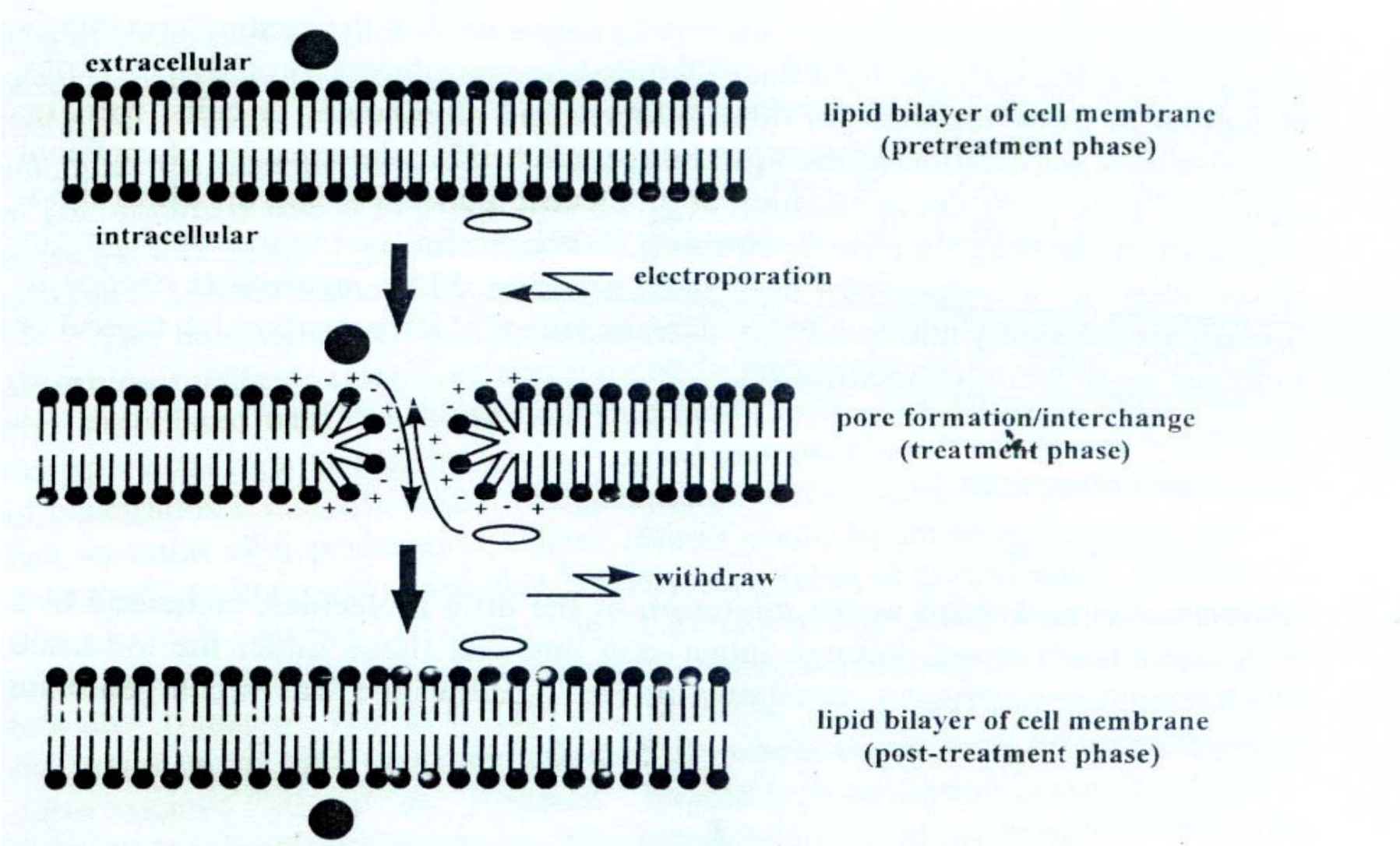
↓ Electrical breakdown

Formation of new and/or enlargement of existing aqueous pathway (transient pores) in SC

↓

Allows the passage of macromolecules from the outside of the cell to the intracellular space
(combination of thermal effect, diffusion, local electrophoresis and/or electroosmosis)

- Can be readily controlled through manipulation of electrical parameters of the pulses delivered and the concentration of agent applied to the skin

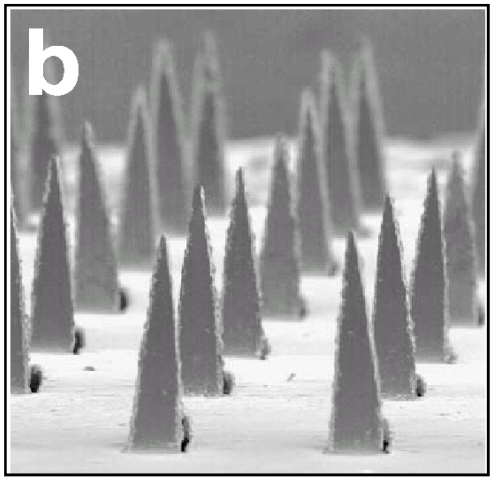


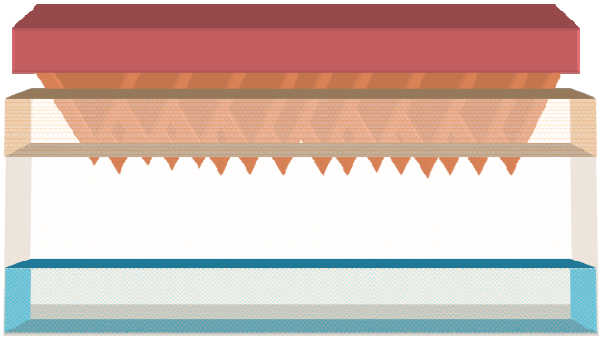
SCHEMATIC REPRESENTATION SHOWING ELECTROPORATION

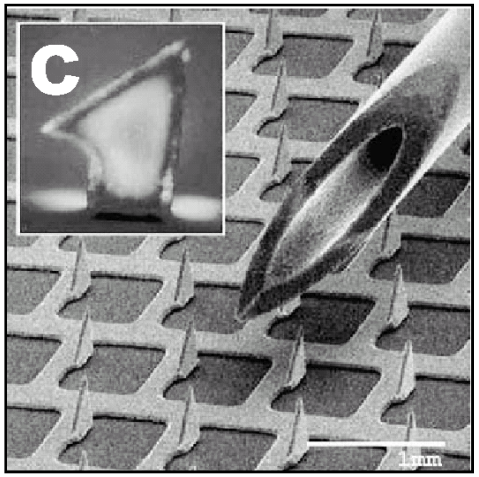
MICROFABRICATED MICRONEEDLES

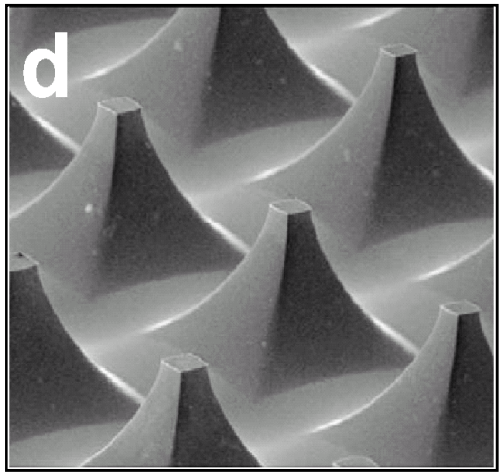
- Designed to create a physical pathway through the upper epidermis to increase the skin permeability
- 10-2000 micron height & 10-50 micron width
- Made up of either silicone or metal
- Needles (approx 400) are fabricated onto arrays
- Solid type or hollow type
- Solid type may be pike shape, or half arrow shape or may be blunted shape

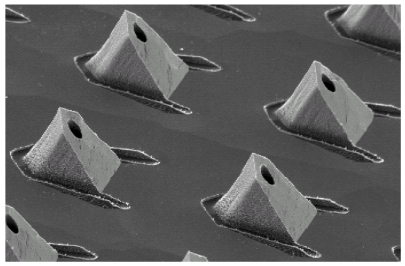
VARIOUS TYPES OF MICRONEEDLES



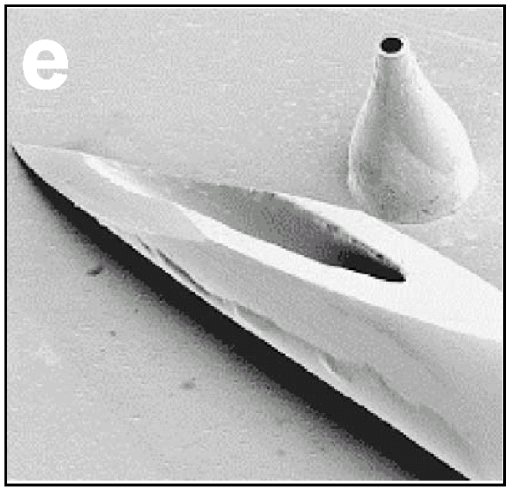




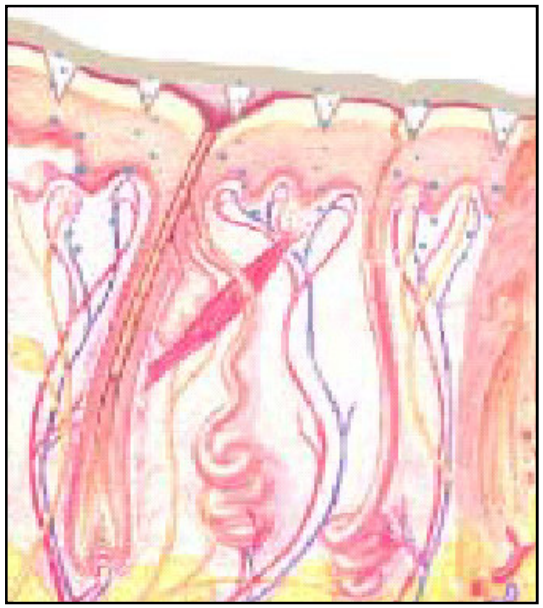




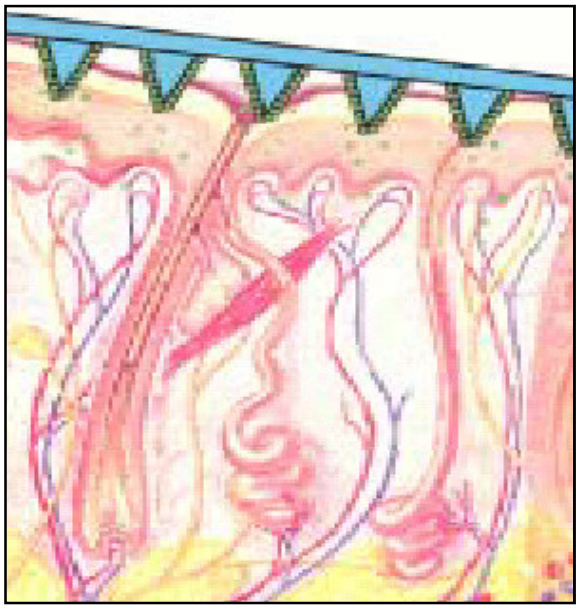
NanoPass's hollow silicon micropyramids.



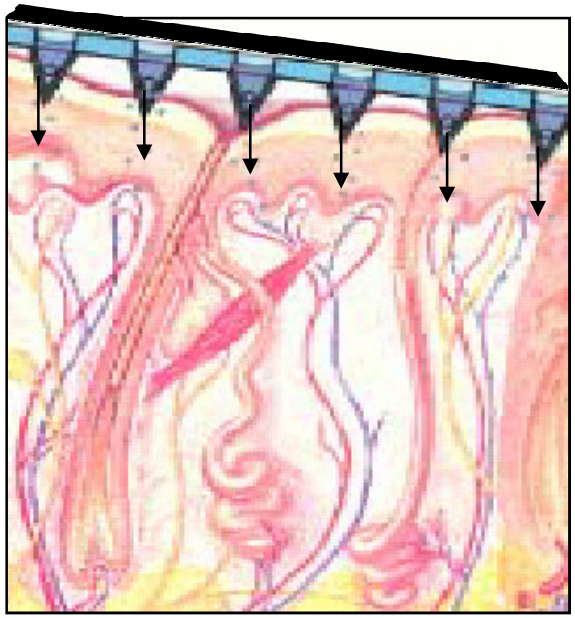
THREE WAYS OF DRUG TRANSPORT THROUGH MICRONEEDLES



Poke with patch



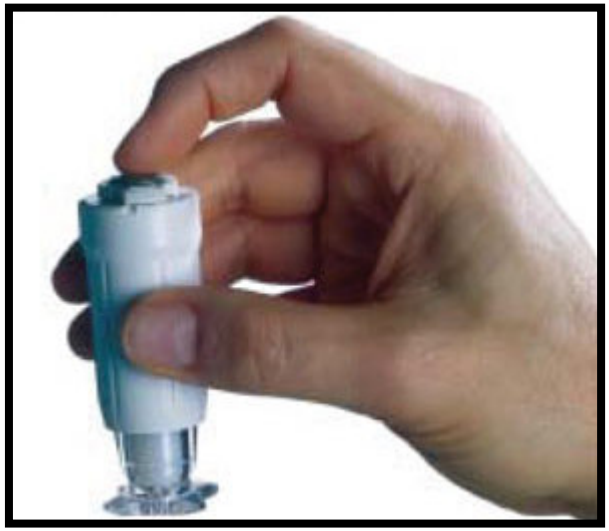
Coat and poke



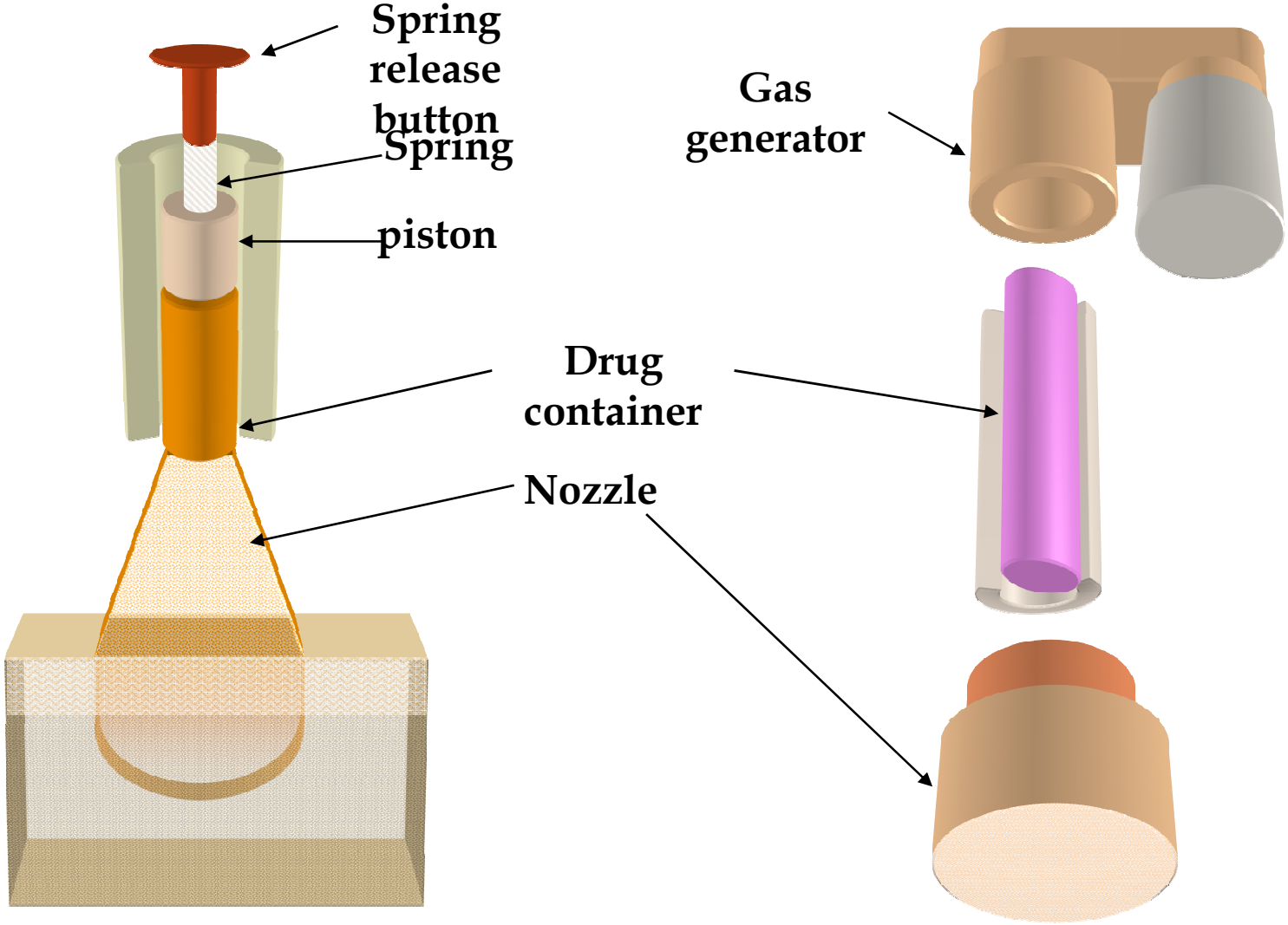
Hollow microneedle

JET PROPELLED PARTICLES (NEEDLE FREE JET DRUG DELIVERY)

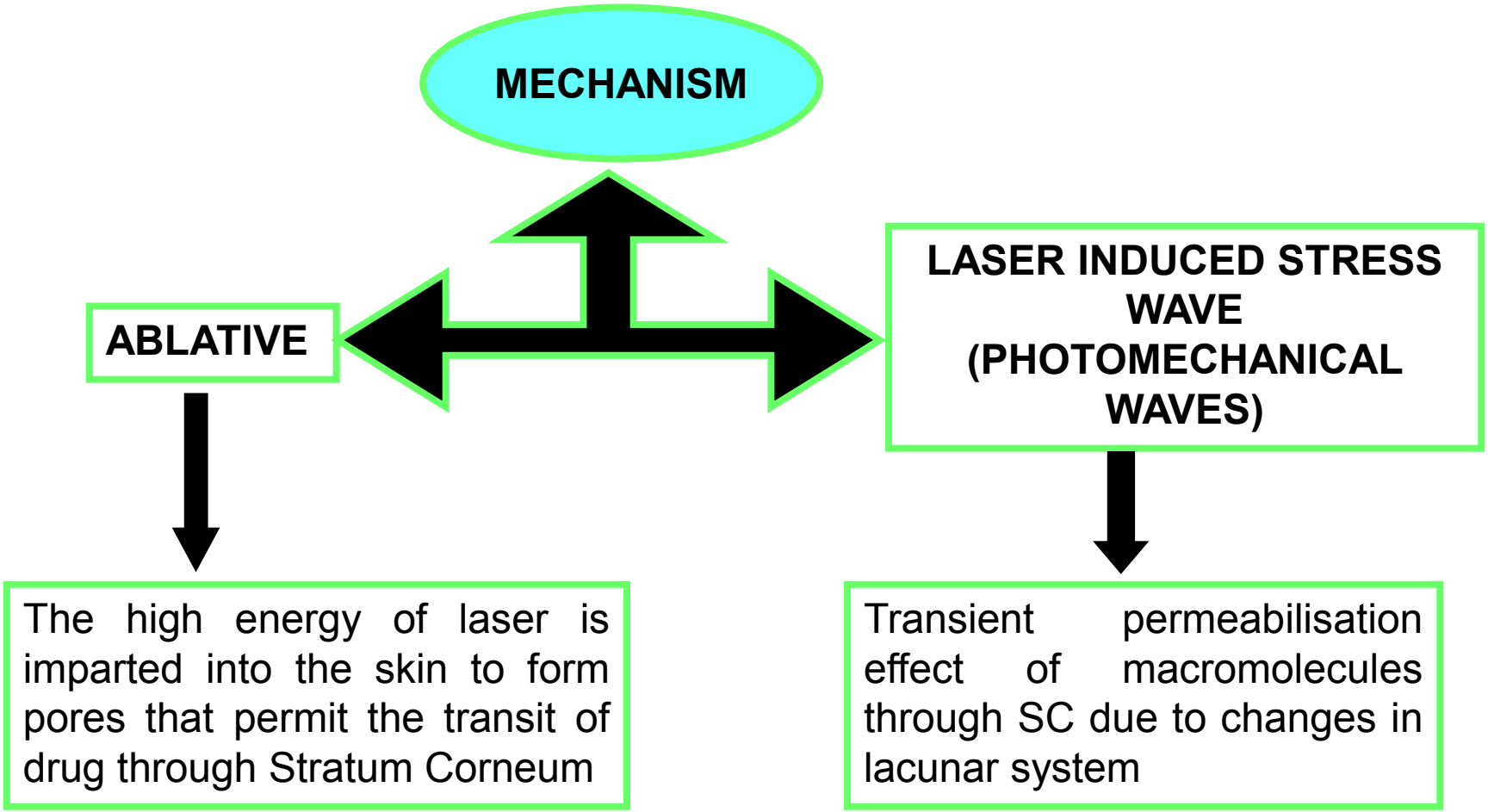
- System is based on delivery of drug (liquid or solid particles) through skin by applying high pressure on the drug.

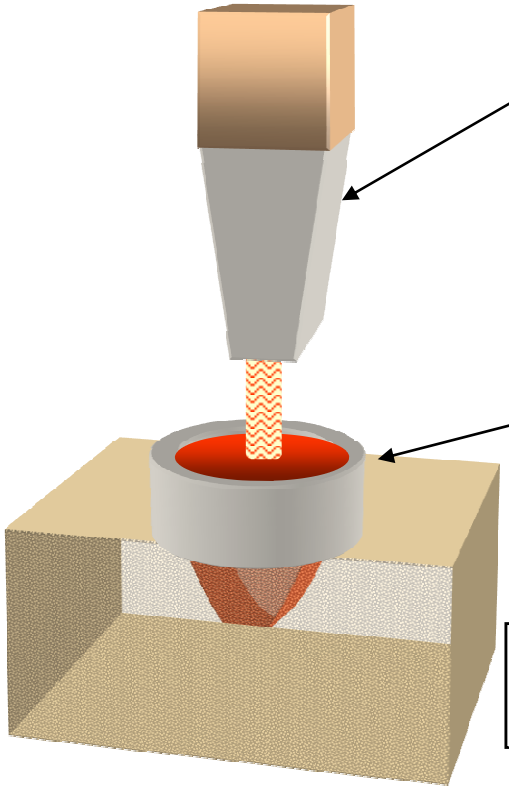


MECHANISMS OF NEEDLE FREE JET TRANSDERMAL DRUG DELIVERY



LASER ASSISTED DELIVERY (LAD)





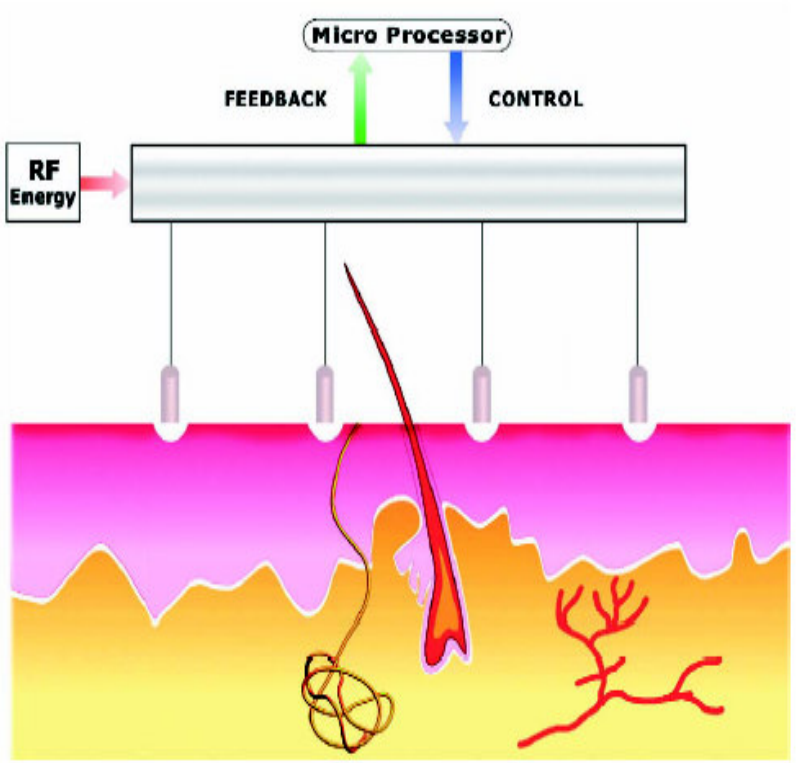
Route of delivery :
1. Transappendageal,
2. Transcellular and
3. Intercellular

The laser is applied to target that is in contact with a drug solution or the drug solution itself

The energy of the laser is strongly absorbed by the target or surface of water and this produces an ultrasonic pressure wave that propagates through the solution to the drug/skin interface

This waves drives the drug through “natural physiological skin pores”

RADIOFREQUENCY-DRIVEN SKIN MICROCHANNELING



Scheme 1. Schematic presentation of RF-microchannels.

The handset system and the microelectrodes array **(ViaDerm, Transpharma Ltd.)**

1. **Creates an array of small microchannels across the SC into the viable epidermis by microablating skin cells.**

2. **The high frequency electrical current conducted through the aqueous medium of the stratum corneum generates heat that brings about an instant removal of cells beneath the electrode.**

3. **Other electrochemical reactions does not take place**

4. **Electroporation may be involved in creation of transient aqueous microchannels**

TRANSFEROSOMES

- Developed by Ceve and coworkers in 1992
- Transferosomes are modified liposomes i.e. they are liposomes with edge activators (sodium cholate)
- Ultradeformable (upto 10^5 times that of an unmodified liposome)
- Well suited for enhancing the transdermal permeation of drug

ADVANTAGES OF TRANSFEROSOMES

- Higher entrapment efficiency protecting encapsulated drug from degradation
- Carrier for low and high molecular weight drugs
- More stable
- High penetration efficiency because of deformability
- Biodegradable and Biocompatible
- Preparation and scale-up preparation is simple
- Site specific local therapy possible
- Minimizes adverse systemic effect

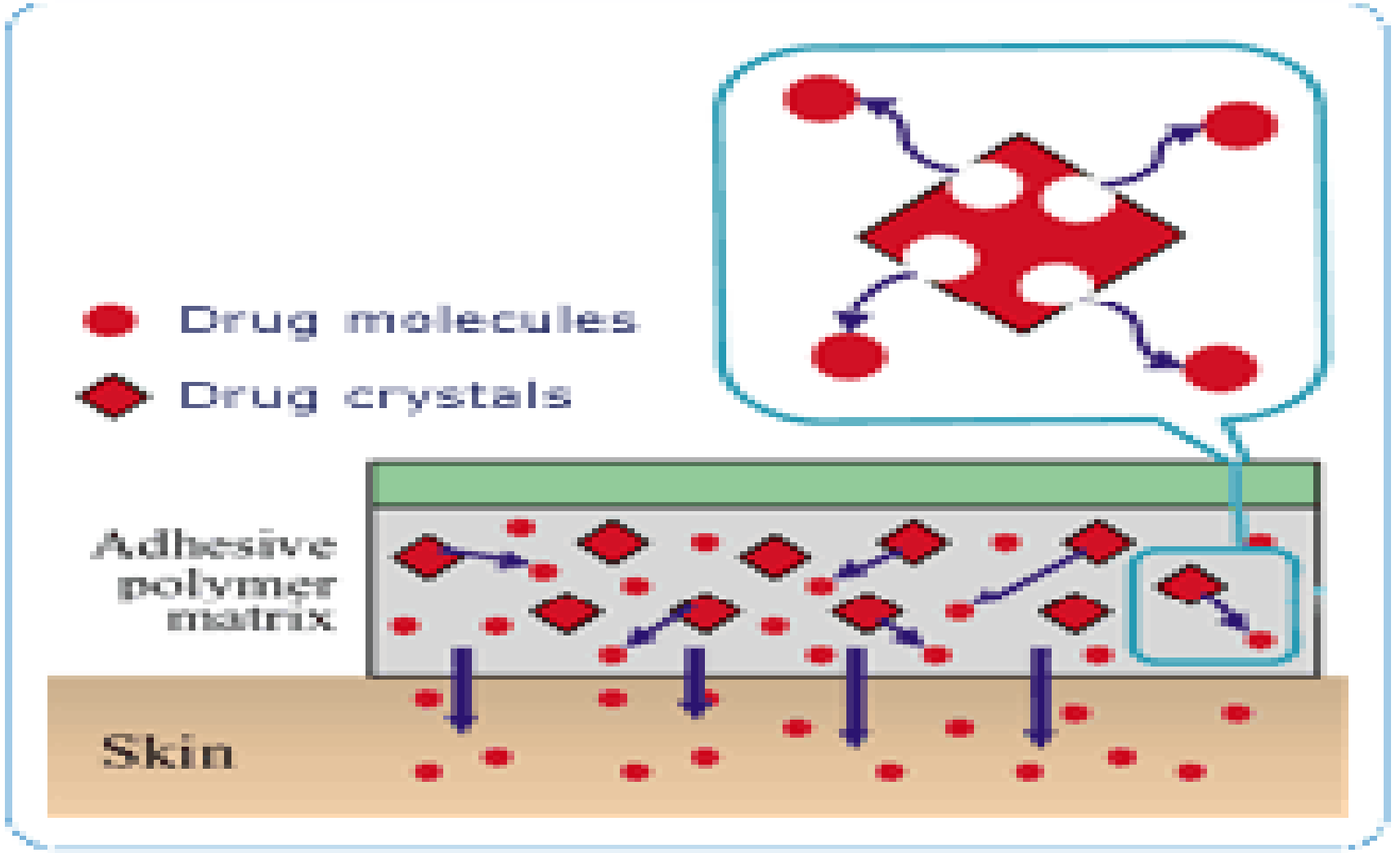
CRYSTAL RESERVOIR TECHNOLOGY

1. **Smaller patches with a more controlled and sustained drug release.**

2. Based on the oversaturation if an adhesive polymer with medication, thus forcing a partial crystallization of the drug.

3. As the skin absorbs the molecular solute, crystals re-dissolve to maintain maximum thermodynamic activity at the site of contact.

4. This technology is employed in the commercial production of the world's only asthma patch, and is one of the most successful patches in the world.


Drug molecules
Drug crystals
Adhesive polymer matrix
Skin

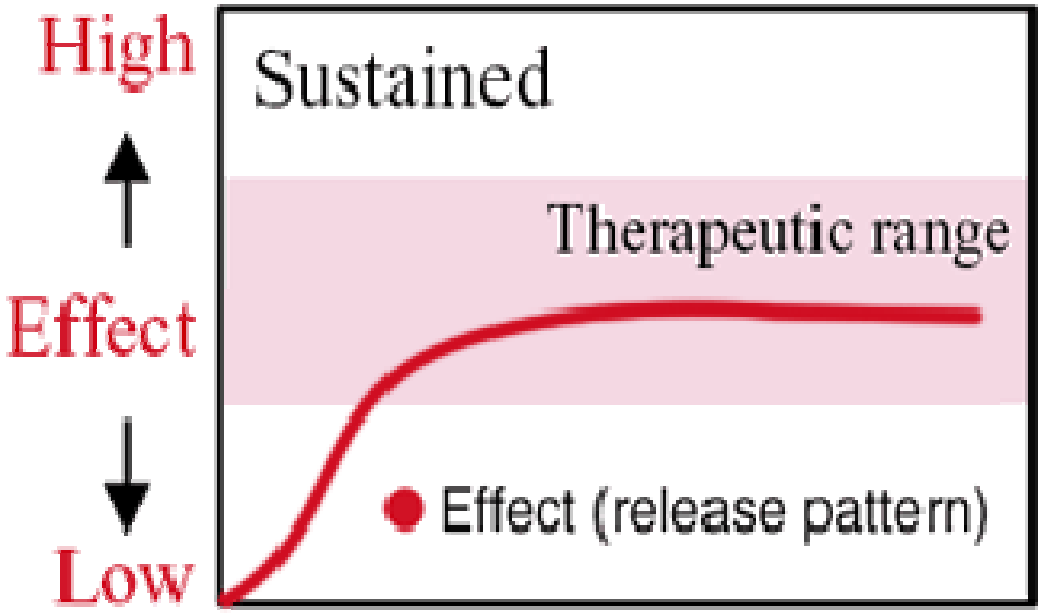
Cont…..

By modifying the concentration of crystals to solute, various patterns of drug release are achieved

- **Sustained release**
- **Burst**
- **Chrono-controlled release**

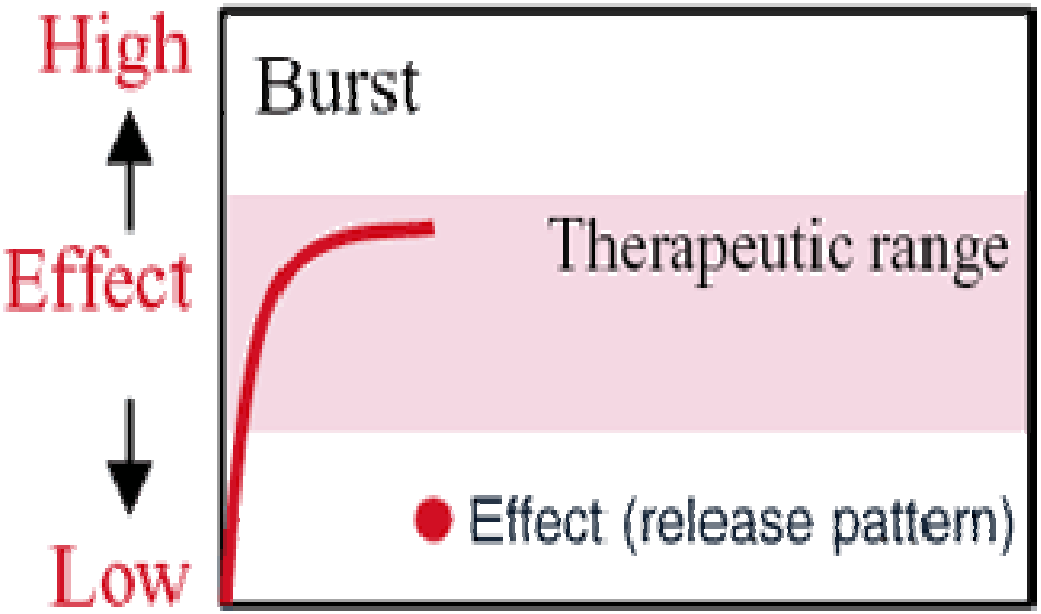
SUSTAINED RELEASE

1.Abundant supply is maintained by dissolving crystals.
2.Blood concentration of drug increase at steady rate and extended plateau.
3.Comparable to intravenous infusion
4.Isosorbide dinitrate TD system (Nitto Denko)



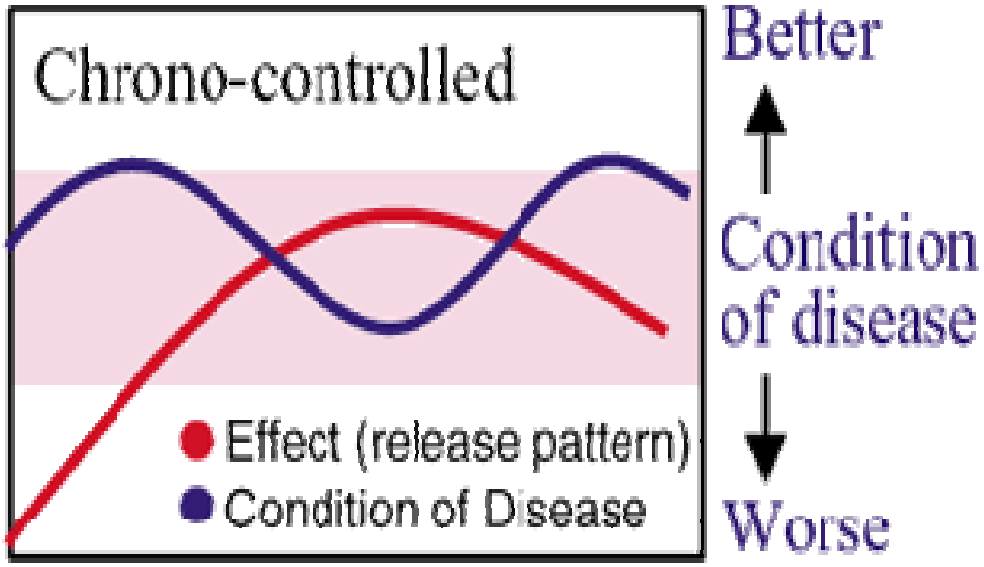
BURST RELEASE

1.Rapid release of drug
2.Blood concentration of drug rises quickly and briefly plateaus.
3.Comparable to injection
4.Lidocaine transdermal patch (Nitto Denko)



CHRONO-CONTROLLED RELEASE

1.Reflects circadian rhythms of the patients.
2.Depends on condition of disease
3.Tulobuterol transdermal patch by Nitto Denko



LIST OF APPROVED TRANSDERMAL PATCH

Table 1 | **Characteristics of transdermal patches***

Active ingredient	Product name	Dose and size of patch	Dose delivered	Clinical indication
Clonidine	Catapres-TTS	2.5–7.5 mg in 3.5–10.5 cm^2	0.7–2.1 mg in 7 d	Hypertension
Ethinyl oestradiol (EO), norelgestromin (N)	Ortho-Evra	0.75 mg EO and 6 mg N in 20 cm^2	0.14 mg EO and 1.05 mg N in 7 d	Birth control
Fentanyl	Duragesic	2.5–10 mg in cm^2	1.8–7.2 mg in 3 d	Analgesia
Lidocaine	Lidoderm	700 mg in 140 cm^2	10–32 mg in 12 h	Post-herpatic neuralgia
Lidocaine (L), epinephrine (E)	Iontocaine	20–50 mg L and 10–25 μg E in 5.7–11.1 cm^2	40 mAmin iontophoresis	Dermal anaesthesia
Nicotine	Habitrol Nicoderm-CQ Nicotrol Prostep	8.3–114 mg in 3.5–30 cm^2	5–22 mg in 16–24 h	Smoking cessation
Nitroglycerin	Nitro-Dur Transderm-Nitro	12.5–160 mg in 5–40 cm^2	1.2–11.2 mg in 12–14 h	Angina
17β-oestradiol	Alora, Climara Esclim, Estraderm FemPatch, Vivelle, Vivelle-DOT	0.39–20 mg in 2.5–44 cm^2	0.075–0.7 mg in 3–7 d	Hormone replacement
Oestradiol (O), norethindrone (N)	CombiPatch	0.51–0.62 mg O and 2.7–4.8 mg N in 9–16 cm^2	0.15–0.20 mg O and 0.42–1.0 mg N in 3–4 d	Hormone replacement
Oxybutynin	Oxytrol	36 mg in 39cm^2	11.7–15.6 mg in 3–4 d	Overactive bladder
Scopolamine	Transderm Scop	1.5 mg in 2.5 cm^2	1.0 mg in 3 d	Motion sickness
Testosterone	Androderm Testoderm TTS Testoderm	10–328 mg in 37–60 cm^2	2.5–6 mg in 1 d	Hypogonadism

*This list contains FDA-approved transdermal patches (not including generics) listed on the FDA website (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/).

POSSIBLE QUESTIONS . . . . . .

1. **What is TDDS ? Why to go for transdermal delivery ? State its limitations.**

2. **What are the possible routes for transdermal drug delivery ? Explain the various stages of transdermal drug delivery.**

3. **Which drug is ideal candidate for TDD ? Mention the classification of transdermal patches. Describe the composition of transdermal patch.**

4. **What are the various process variables and the intermediate test carried out during the manufacturing of transdermal system ?**

5. **What are the evaluation tests carried out on final transdermal product ? Write details about Adhesion testing.**

6. **Mention various methods for maximising transdermal permeation of drug. According to you which is the best enhancement technique and write details about it.**

7. **Write a note on Electrically Based Enhancement Technique in detail.**

8. **Write a note on Iontophoresis and Phonophoresis.**
9. **Mentional details about Electroporation and Radiofrequency as transdermal enhancement technique.**

10. **What do you mean by Ultradeformable Liposomes ? Write detail mechanism of its transdermal permeation enhancement.**

11. **Write a note on Minimally Invasive System for transdermal permeation enhancement.**

WEBSITES SEARCHED

www.doyenmedipharm.com
www.noven.com
www.fda.gov
www.drugdeliverytech.com
www.pharmtech.com
www.drugdiscoverytoday.com
www.nature.com
www.uspharmacist.com


WHEN WE'RE NO
LONGER ABLE TO
CHANGE A SITUATION,
WE'RE CHALLANGED TO
CHANGE OURSELVES.
Thank you...