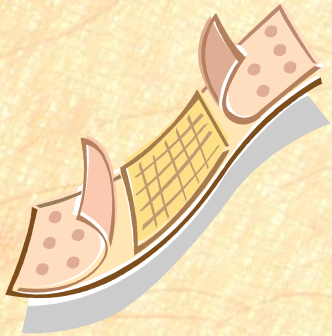
Dermal and transdermal drug delivery systems



University of Pécs, Institute of Pharmaceutical Technology and Biopharmacy

Main properties of our skin

Our organ is bordered from the external world by our skin (c*utis, derma)* , therefore it plays a very important role to maintain self balance.

Adult skin:

average surface: 1,5 m^2.

average mass: 12 kg (8-10% of the body mass)

At body orifices continues as mucosa to the internal cavities of the organ such as: mouth, rectum.

Main properties of our skin

The histological, cytological structure, and order of the skin empowers to do wide range of takes.

Principal physiological features of the skin:

1) Mechanical protection,
2) Chemical protection, barrier function (against chemicals and dehydration),
3) Protection from microorganisms (acid coat),
4) Light protection (pigment production),
5) Vitamin D production in the epidermal layer,
6) Thermoregulation (vessels, sweating),
7) Metabolism,
8) Excretion,
9) Perception of external stimulus (heat, touch, pain),
10) Absorption through the skin.

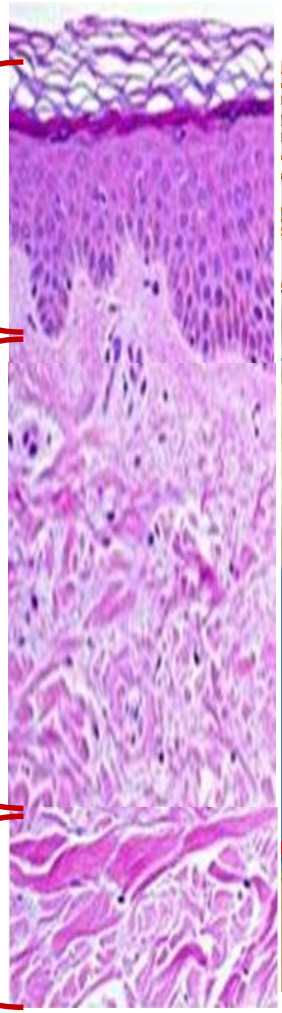
Structure of the skin

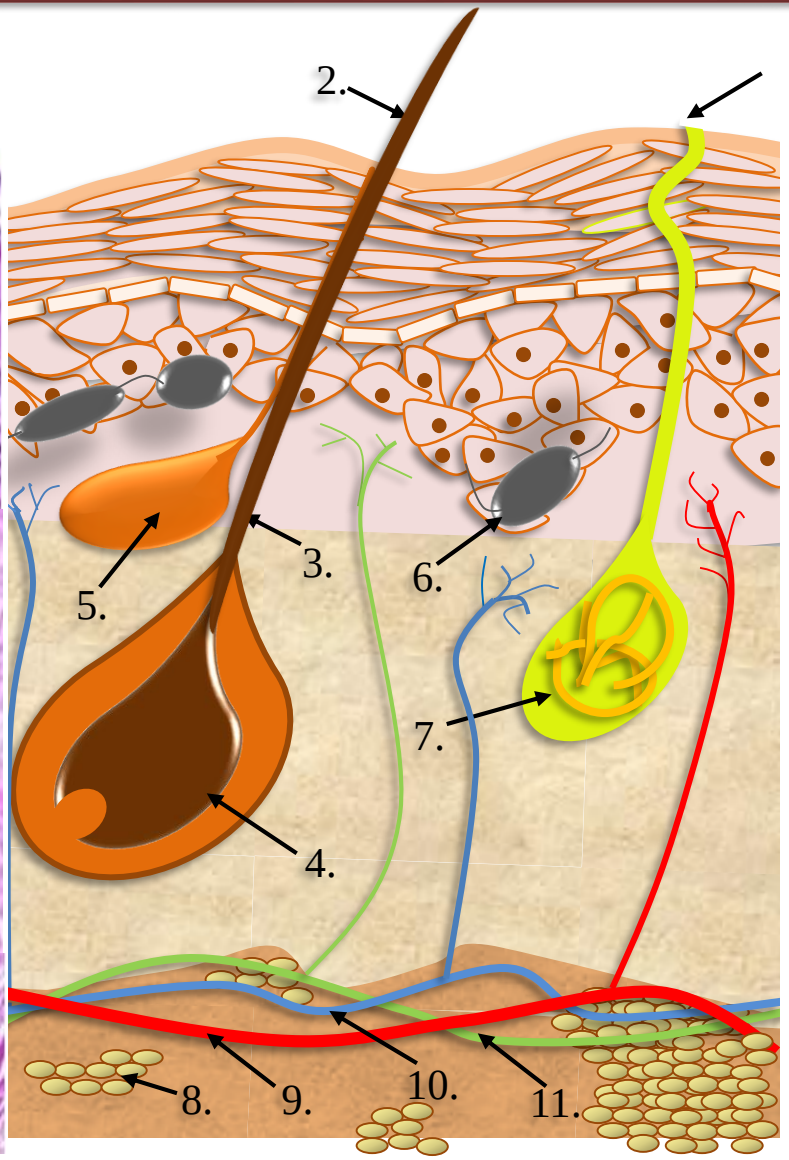
Stucture and structural elements of the skin

epidermis
0.05-1.5 mm

dermis
~2 mm

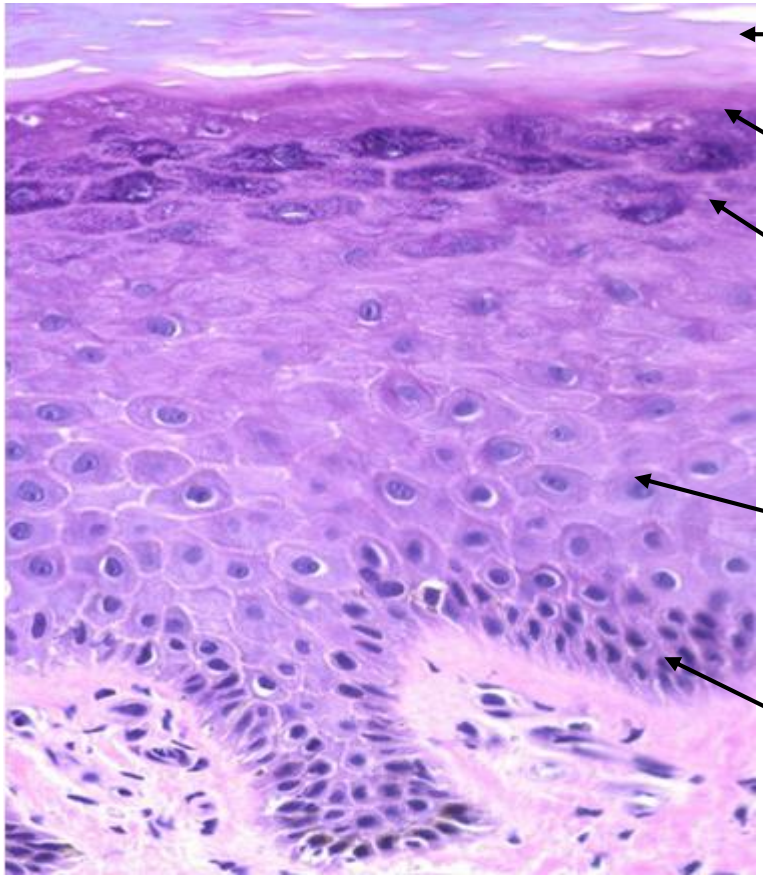
hypodermis





1. porus
2. pilus (hair)
3. folliculus pili (follicle)
4. bulbus pili (hair follicle)
5. glandula sebaceae (sebaceous gland)
6. melanocyta (melanoma cell)
7. glandula sudoriferae (sweat gland)
8. subcutaneous fat
9. arteriola small artery
10. venula Small vein)
11. nervus (nervus)

The epidermis

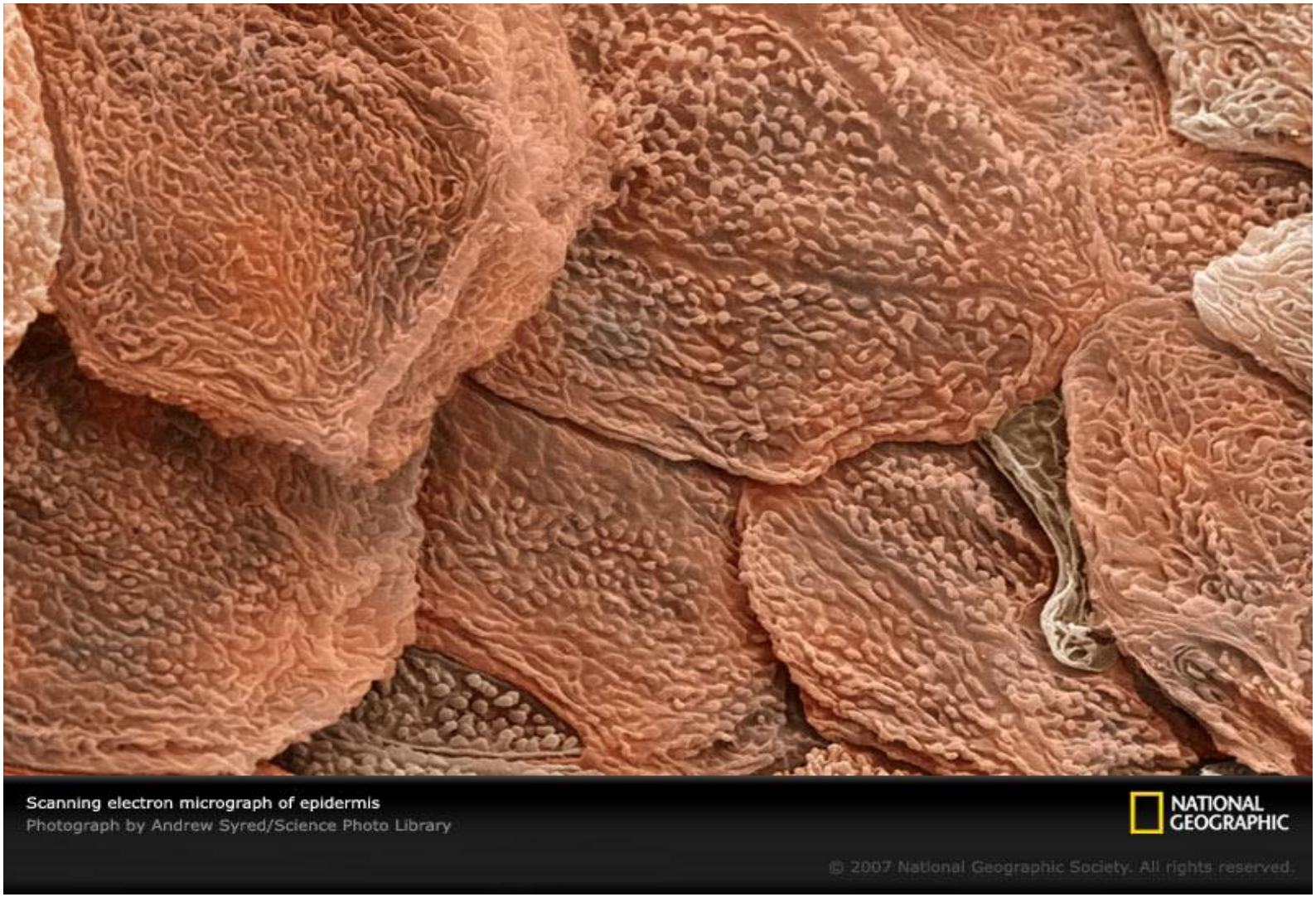


layer	function
Thorny layer (stratum corneum)	permeable barrier, ceratin
Light protection layer (stratum lucidum)	Intensive scattering effect
Granular layer (stratum granulosum)	Precurzors of lipids
Spiny layer (stratum spinosum)	ceratinisation
Layer of basal cells (stratum basale)	Cell proliferation (skin colour-melanin)

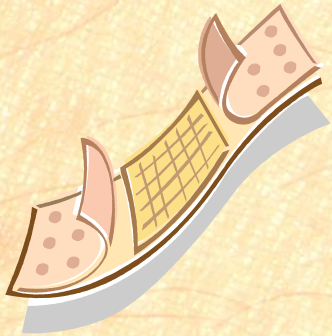
The epidermis is the layer of skin has no vessel in it (non-vascularisated), which has free nerve endings (FNE).

Stratum corneum

The thorny squamous because of its protective function,is usually difficult to go through for extraneous materials.

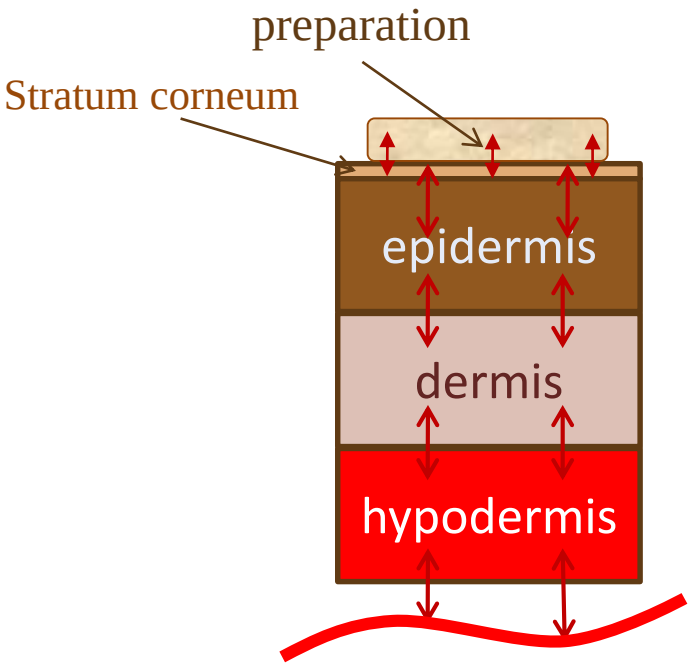


The speed of absorption



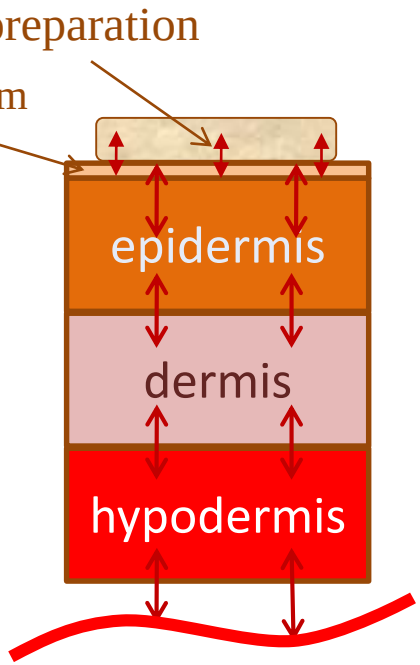
LADME system

- **Liberation**
- **Penetration**
- **Permeation**
- **Absorption**
- **Distribution**
- **Metabolism**
- **Excretion**



Absorption

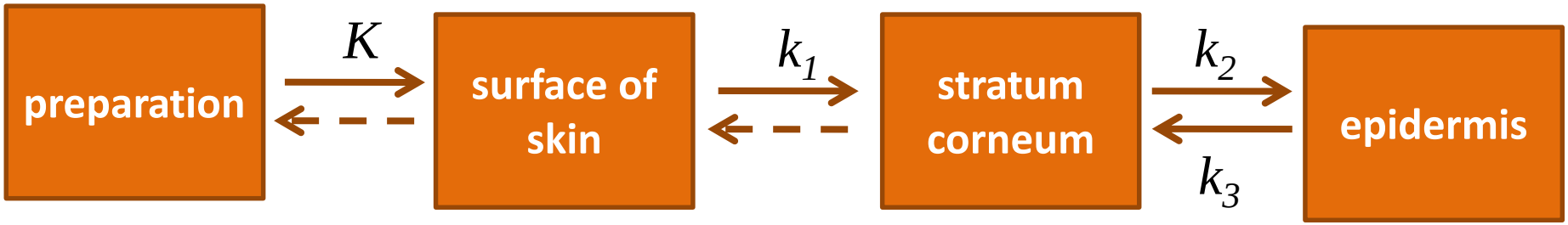
Absorption model



- Diffusion of API from inside of preparation into stratum corneum,
- Interaction between API and stratum corneum,
- Diffusion through stratum corneum (through lipophilic corneum to more hydrophilic epidermis) ,
- Pass through the non-vascularisated layers to the capillaries
- Absorption into capillaries

Absorption

Absorption model



K	diffusion of API inside the preparation
k_1	diffusion through stratum corneum
k_2	transport into epidermis
k_3	reverse flow
k_1	diffusion through stratum corneum

The accumulated quantity in stratum corneum of API is determinated by k_1, k_2 , k_3 and K.

The proportion of k_3/k_2 is the effective distribution coefficient between the two layers(stratum corneum and epidermis).

Absorption

The skin permeablitiy coefficient (P_{derm})

The mechanism of absorption can be interpreted, that the skin is a two-layered membrane, which upper layer is lipophilic the lower is hydrophilic.

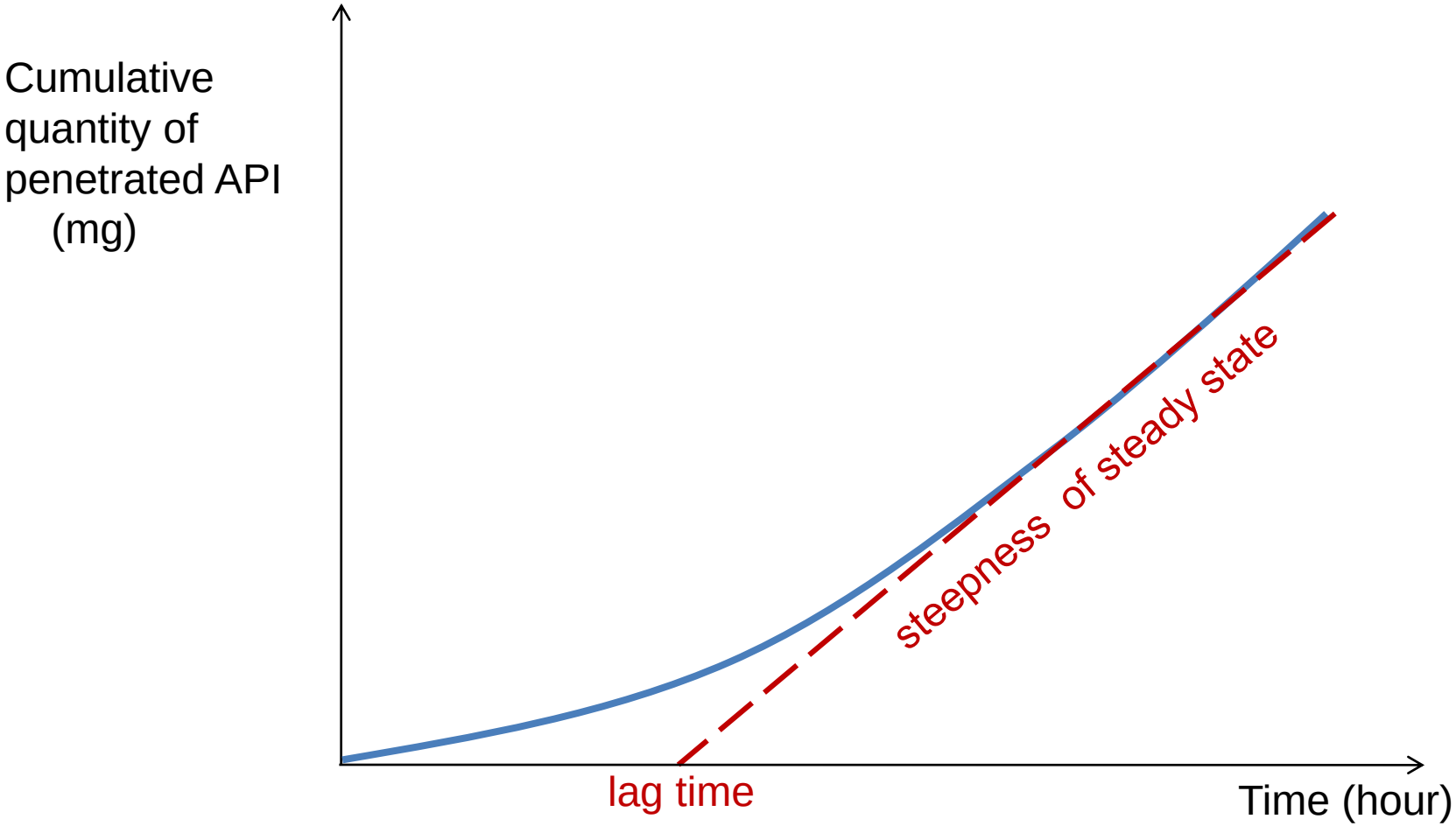
$$P_{derm} = \frac{\delta_h \delta_l}{k h_h \delta_l + h_l \delta_h}$$

P_{derm} = *skin permeability coefficient*

k = distribution coefficient between lipophilic and hydrophilic layer,
δ_h = diffusion coefficient in the hydrophobic layer,
δ_l = diffusion coefficient in the lipophilic layer,
h_h = thickness of the hydrophilic layer
h_l = thickness of the lipophilic layer

Absorption

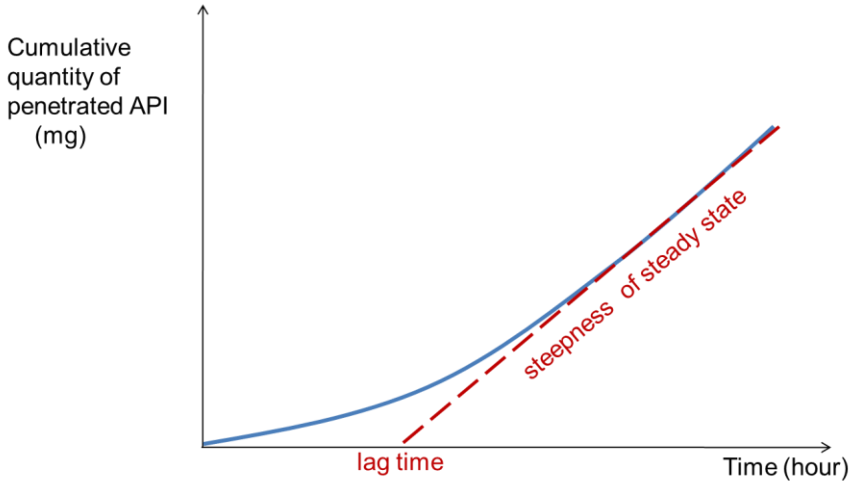
Flux in the balance state of penetration (J_{ss})



Absorption

Flux in the balance state of penetration (J_{ss})

$$J_{ss} = \frac{KD}{h}(c_o - c_i)$$



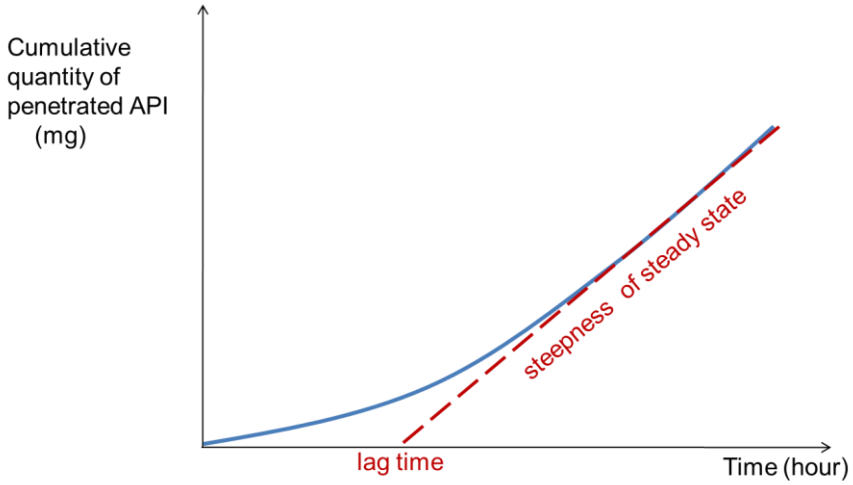
J_{ss} = flux per unit area

K = distribution coefficient (preparation -stratum corneum)
D = diffusion coefficient in stratum corneum
h = thickness of diffusion layer (stratum corneum)
c_o = concentration of API placed on skin ($t=0$)
c_i = concentration of API placed in skin($t=t_i$)

Absorption

Flux in the balance state of penetration (J_{ss})

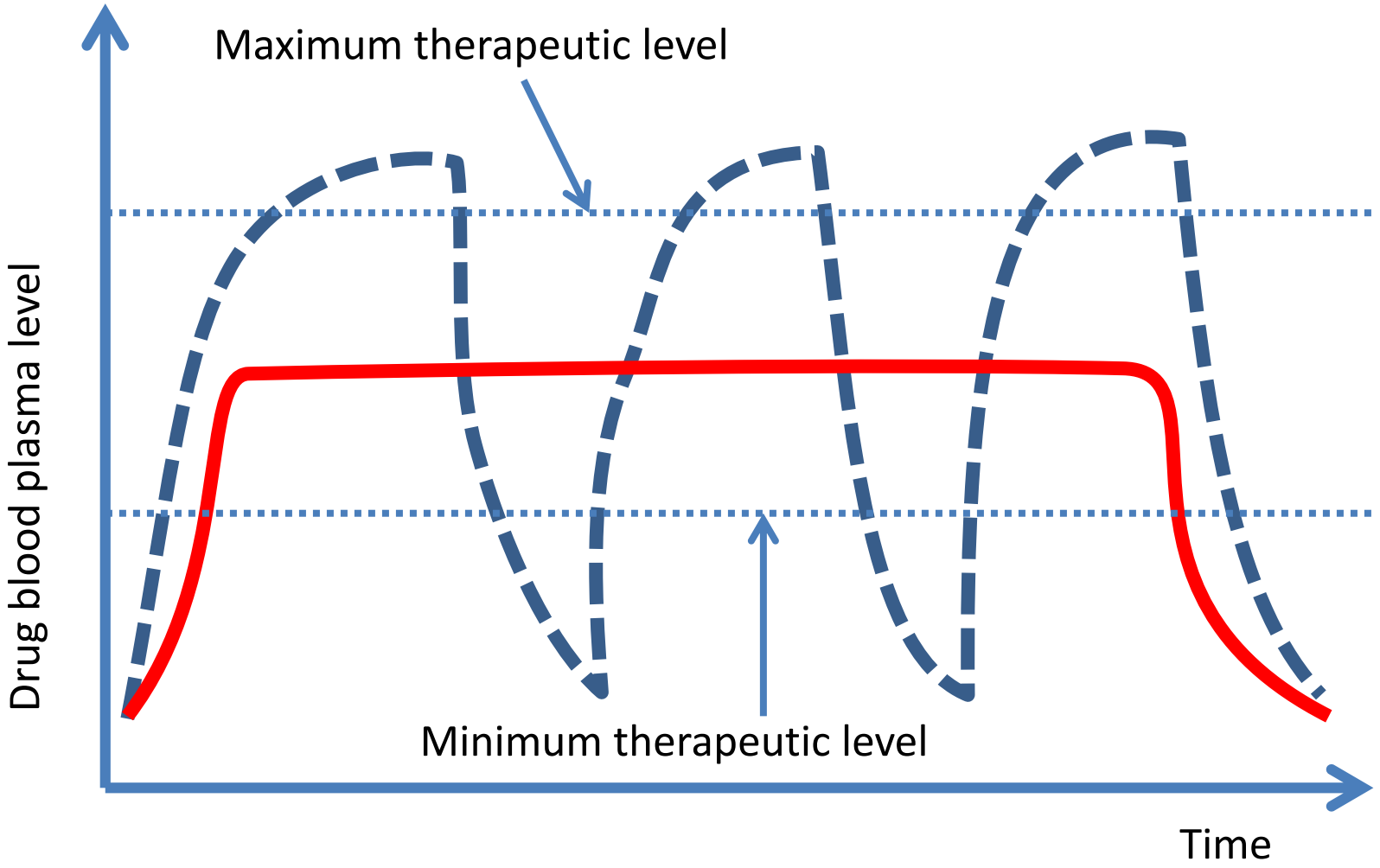
$$J_{ss} = P_{derm}\Delta c$$



P_{derm} = permeabilitation coefficient

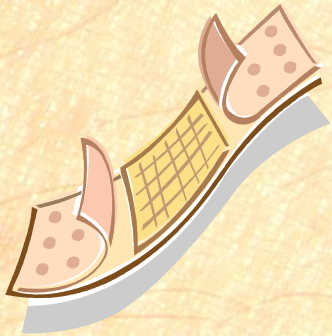
ΔC = concentration gradient

Absorption



Oral and Transdermal dose

Routes of absorption

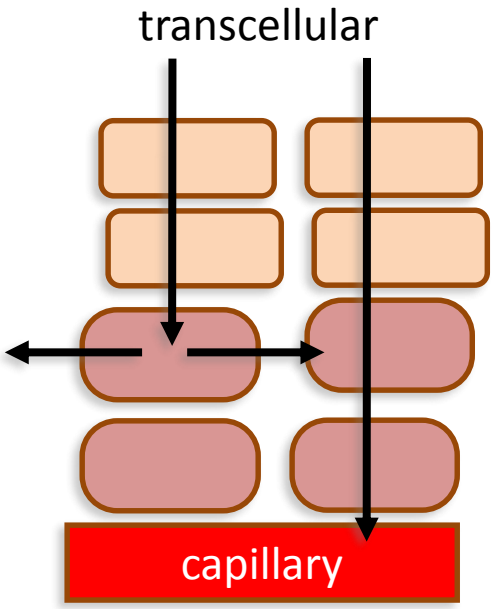


Routes of absorption

1) In transcellular way,

2) In paracellular way,

3) Via skin appendix



Through the lipo-protein layer of the stratum corneum can get into dermis (and circulation).

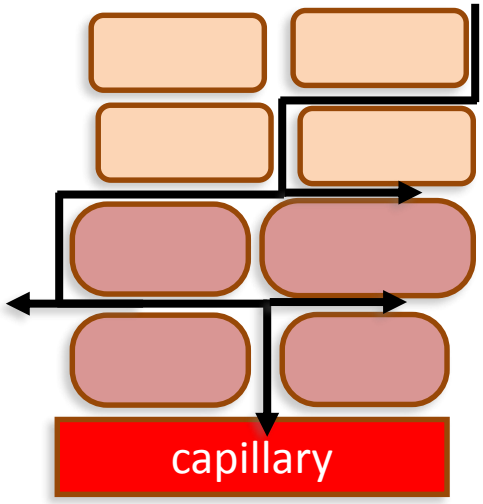
Routes of absorption

1) In transcellular way,

2) In paracellular way,

3) Via skin appendix

Paracellular way

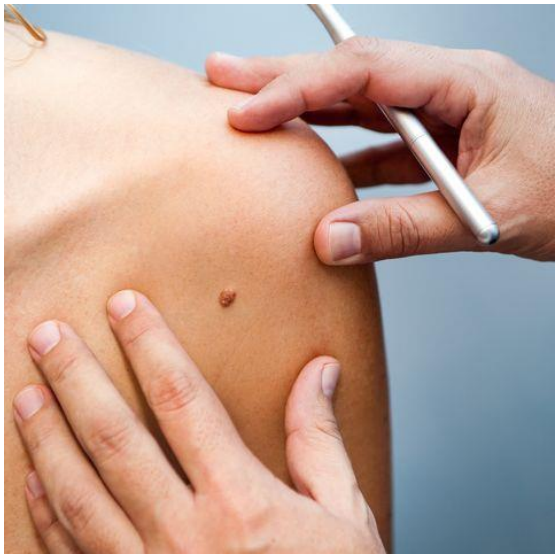


The API gets through among the cells into dermis (or circulation).

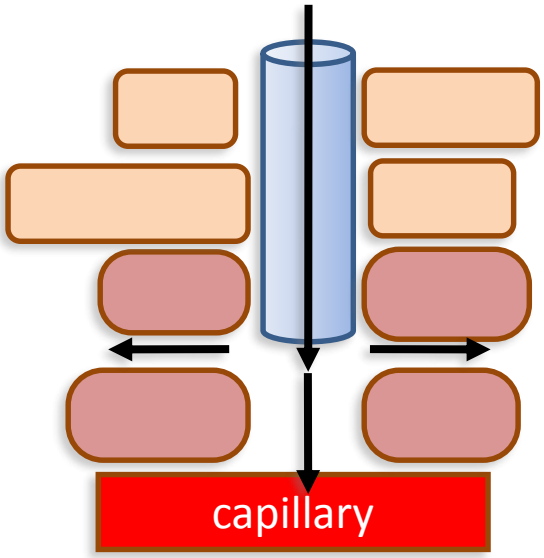
The extracellular space consists of lamellar structured lipids (cholesterol, ceramids, free fatty acids).

Routes of absorption

1) In transcellular way,
2) In paracellular way,
3) Via skin appendix



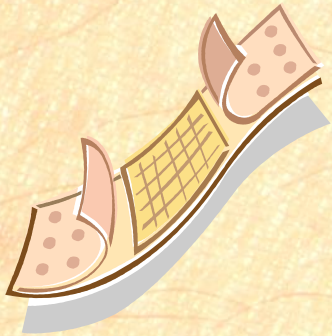
Skin appendix



The system of hydrophilic and hydrophobic channels helps the penetration of skin.

The APIs go through hair follicles, sebaceous glands, sweat glands into dermis (and circulation).

Absorption and its determining factors



Absorption determining parameters

Main parameters

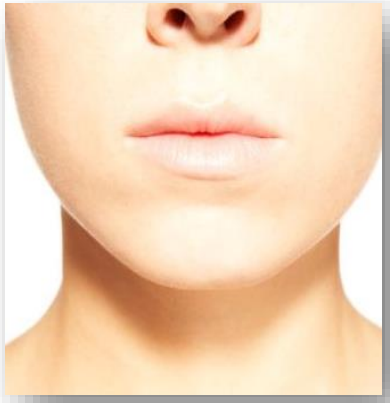
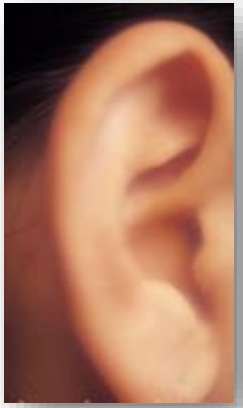
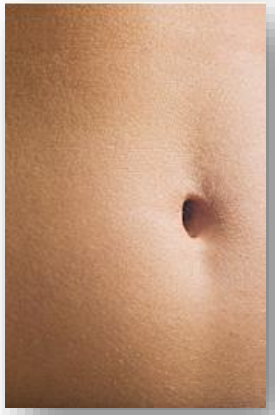
1) age,
2) pH,
3) temperature,
4) humidity,
5) vehicles,
6) structure integrity of skin (injury)

Absorption determining parameters

Thickness of skin

Thickness varies,

- thinnest is on eyelids: 0,5 mm,
- thickest is on palms and soles: 1-5 mm.


Absorption determining parameters

Thickness of skin

Relative absorption of hidrocortison:

sole 1
back 12
forehead 43

Absorption determining parameters

Age

The surface, structure and thickness of all and all single layers of skin varies according to age.

Through the new-borns' thin layered skin even toxic amount of APIs can absorb. (*for example hexachlorophene can cause CNS toxicity.*)

Absorption determining parameters

Age

With age
- the thickness,
- hydration,
- composition,
- blood supply and
- absorption ability can change.

Over time the **stock of fibers enriches** compared to extracellular area in dermis.

When the water content of skin decreases **under 10%** it becomes dry and wrinkled.

The structure of skin loses its collagen content after menopause, because of hormonal control of the body.

Absorption determining parameters

pH of skin

The neutral pH of skin is between 5,4 and 5,9.

The acidic pH is not just important because of creating the protective layer, but the chemical interactions are also carried out perfectly in this range of pH.

If the pH of skin changes to basic (for example exaggerated usage of soap), then the physiological balance of skin fails (the protection against bacteria declines, thus infection can occur).

Absorption determining parameters

Water content

The water content of basal layer is 70% , thorny layer 30%, surface of skin 10%.

The hydration of skin and with this, penetration can be risen, if the skin is covered to prevent evaporation.

In this case, **water content of epidermis can be increased** with even **40-50%** and swelling can cause the loosening of cells.

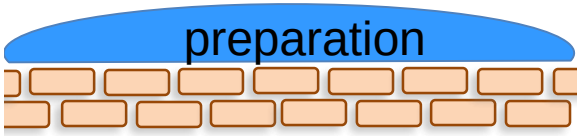
For example absorption of lipophilic corticosteroids can be increased by even 10 fold .

Absorption determining parameters

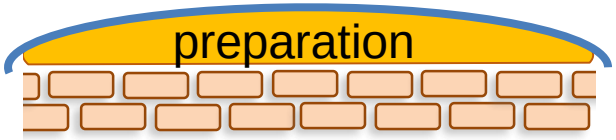
Water content

The hydration of skin upper layers can be achieved by:

1.) with **waterproof/impermeable preparation** (i.e. *hydrocarbon-based ointment)*



2.) with the cover of a part of skin with a **water resistant** layer (i.e. occlusive patch)



Absorption determining parameters

Skin temperature

The increase in skin temperature significantly increase **percutaneous absorption**.

The reason of this phenomenon is that the vasodilatation of vessels cause the **rise of blood circulation**, and partly the **decrease of viscosity** of the basic preparation and lipoid materials in skin.

Absorption determining parameters

The charge of molecules

On the surface of skin there is an „**electrophysiological barrier**”, namely a polar membrane, with **negative charge** on external surface.

The penetration of electrolytes are **inhibited** strictly through the barrier.
Nevertheless **cations can go through** the membrane, but the way forward is embarrassed by electrostatic force.

Absorption determining parameters

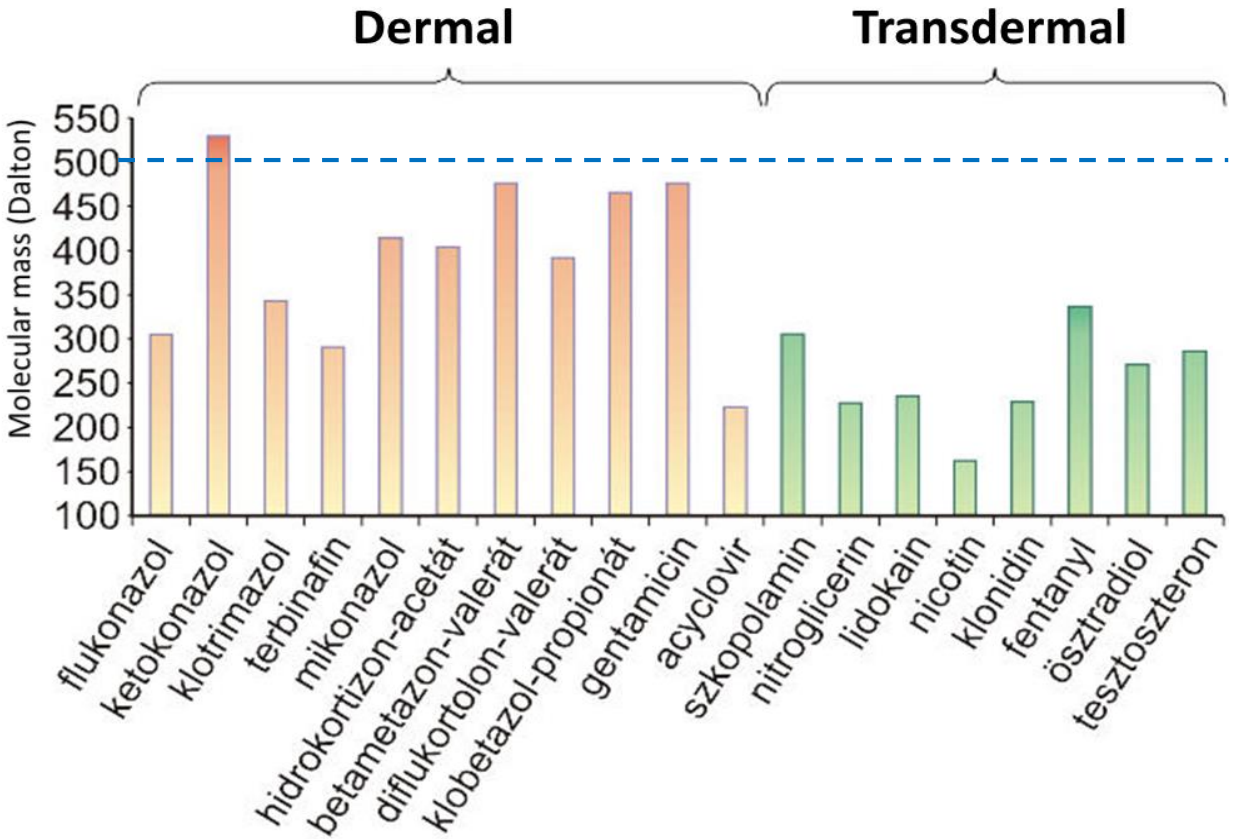
Lipophilicity of skin

The cell membrane is basically **lipoid** natured, therefore **lipid-soluble materials can penetrate** through this much more easier. (Lipoid barrier).

The absorption of the molecules with high lipoid-water distribution coefficient is considerable via skin.

Absorption determining parameters

Mass of molecules



Boss et al. established that, substances with less than 500 Dalton can penetrate through skin. For example cyclosporine with 1202 Dalton was not provided to be effective in psoriasis. This rule is valid to allergens too.

Dermal drug delivery systems

Main specifications

Preparation intended to skin surface is used to treat a particular site of skin or skin mucus, to aim a local or absorption effect, but it can also have skin softening or protective effect.

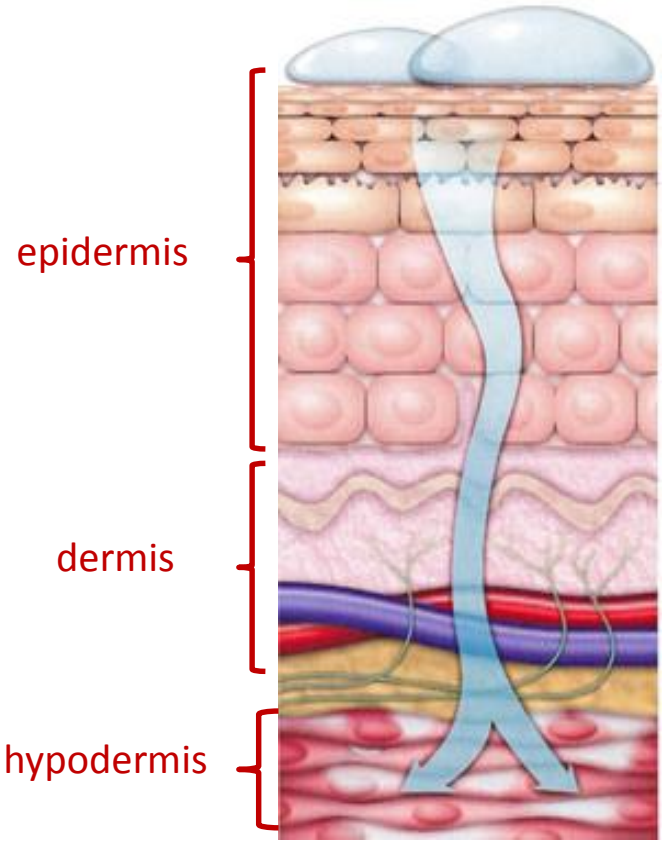
Categorization

The preparation intended to treat skin surface can be categorize according to:

1) solutions,
2) suspensions, emulsions,
3) ointments,
4) cremes,
5) gels,
6) pastas,
7) compressing ointments,
8) patches (conventional),
9) aerosols, foams,
10) powders.

Dermal drug delivery system

Contol of the absorption



1. API

   a) Type (appropriate lipophilicity water-octanol distribution coeff. =10-1000)
   b) Molecular mass,
   c) Quantity (concentration)

2. Vehicle

   a) Type (lipophilic / hydrophilic),
   b) Absorption assisting materials (alcohols, surfactants, DMSO, pirolidin derivatives..)

3. Mode of application

   a) surface,
   b) intensive rubbing (local hyperaemia),
   c) ensuring humid environment (pl. bandage)

Transdermal drug delivery systems

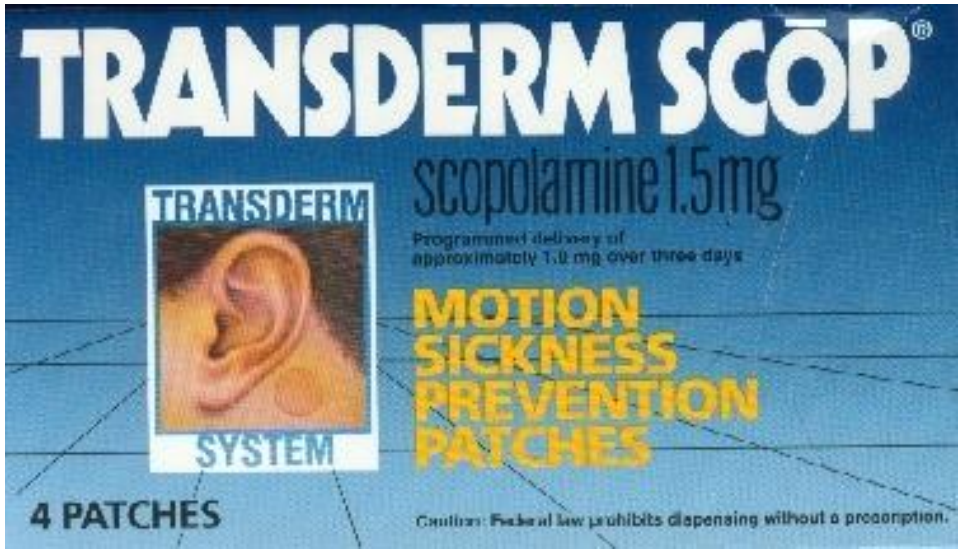
Transdermal drug delivery system

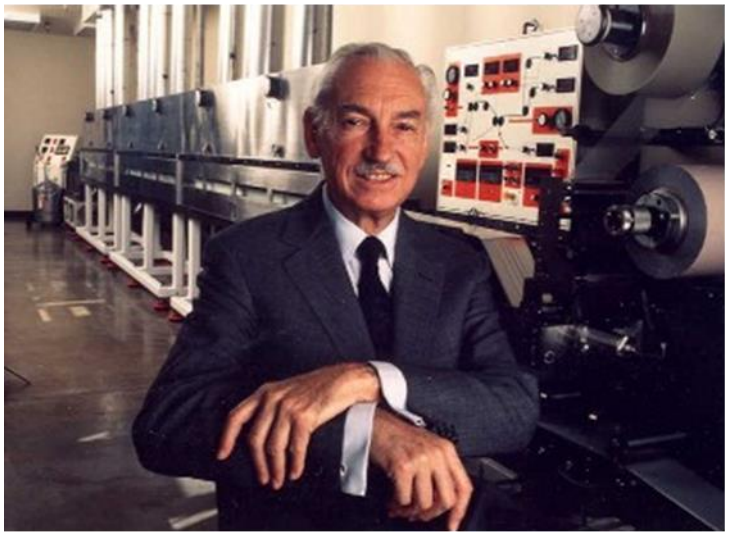
Transdermal Drug Delivery System, TDDS

These preparation are used on the skin to achieve an absorbing **controlled systemic effect**.

Their research has been started mostly in the end of 1970's.

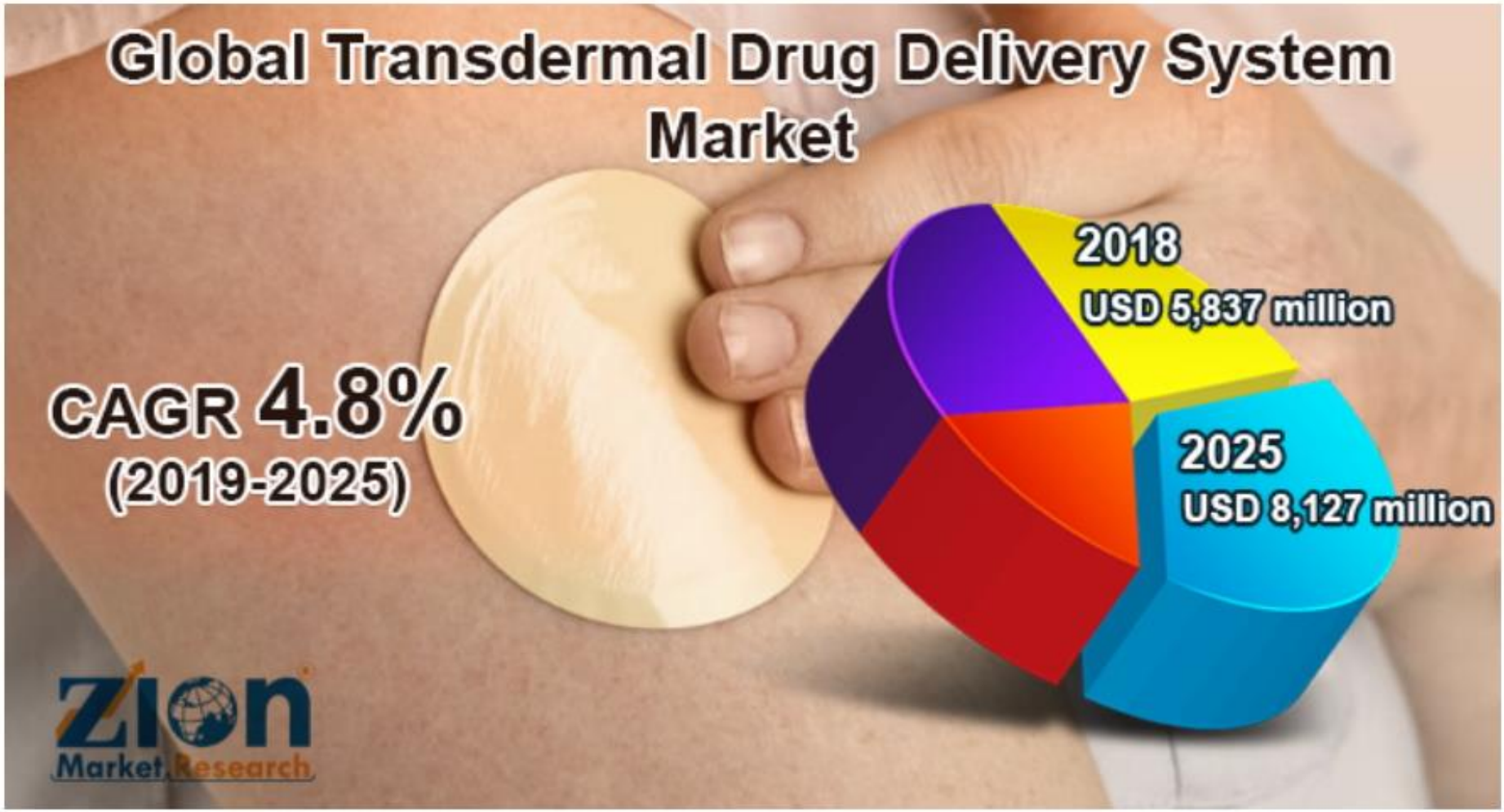
Dr. Alejandro Zaffaroni





ALZA Corp.

Transdermal drug delivery system



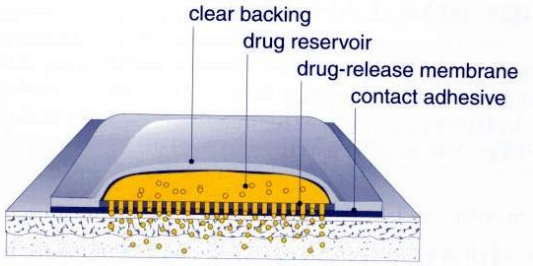
Transdermal Drug Delivery System Market Global Industry Revenue To Surge To US$ 8,127 Million By 2025

BY HIREN SAM ON SEPTEMBER 9, 2019

Transdermal drug delivery system

Transdermal drug delivery system

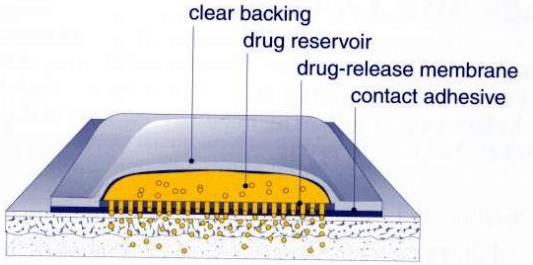
Advantages



1. Systemic effect can be achieved,
2. Allows precise dosing,
3. No first pass effect,
4. Spare the GI tract, and no food interaction can occur,
5. Liberation is not influenced by consumed food,
6. Allow to treat patients suffering for nausea or vomiting ,
7. Simple dosing method,
8. Decreases the illness consciousness

Transdermal drug delivery system

Disadvantages



1. The absorbing surface is small,
2. Low rate of APIs are able for absorption via skin in adequate amount
3. At the first application saturation time is needed, until the amount of API reach the therapeutically sufficient plasma concentration
4. In case of long term use sometimes skin sensitivity can happen,
5. The manufacturing costs are usually higher because of more complicated technology

Transdermal drug delivery system

Their application

The transdermal drug delivery systems can be specially beneficial in the cases of therapy of diseases, which have to be treated as a cure, constantly and long term medication is needed.

- diabetes,
- arteriosclerosis,
- allergy,
- cardiovascular diseases (e.g. hypertension, angina pectoris, heart rate)
- rheumatic diseases,
- hormone therapy,
- contraception,
- CNS durgs,
- analgesics (e.g. cancer dieases),
- consumer products
- others, e.g. prepararions againt smoking and alcohol consuming

Transdermal drug delivery system

Applied dosage possibilites

1. patches,
2. iontophoresis,
3. ultrasound,
4. micro needle,
5. high speed „jet” injections
6. nanostructures

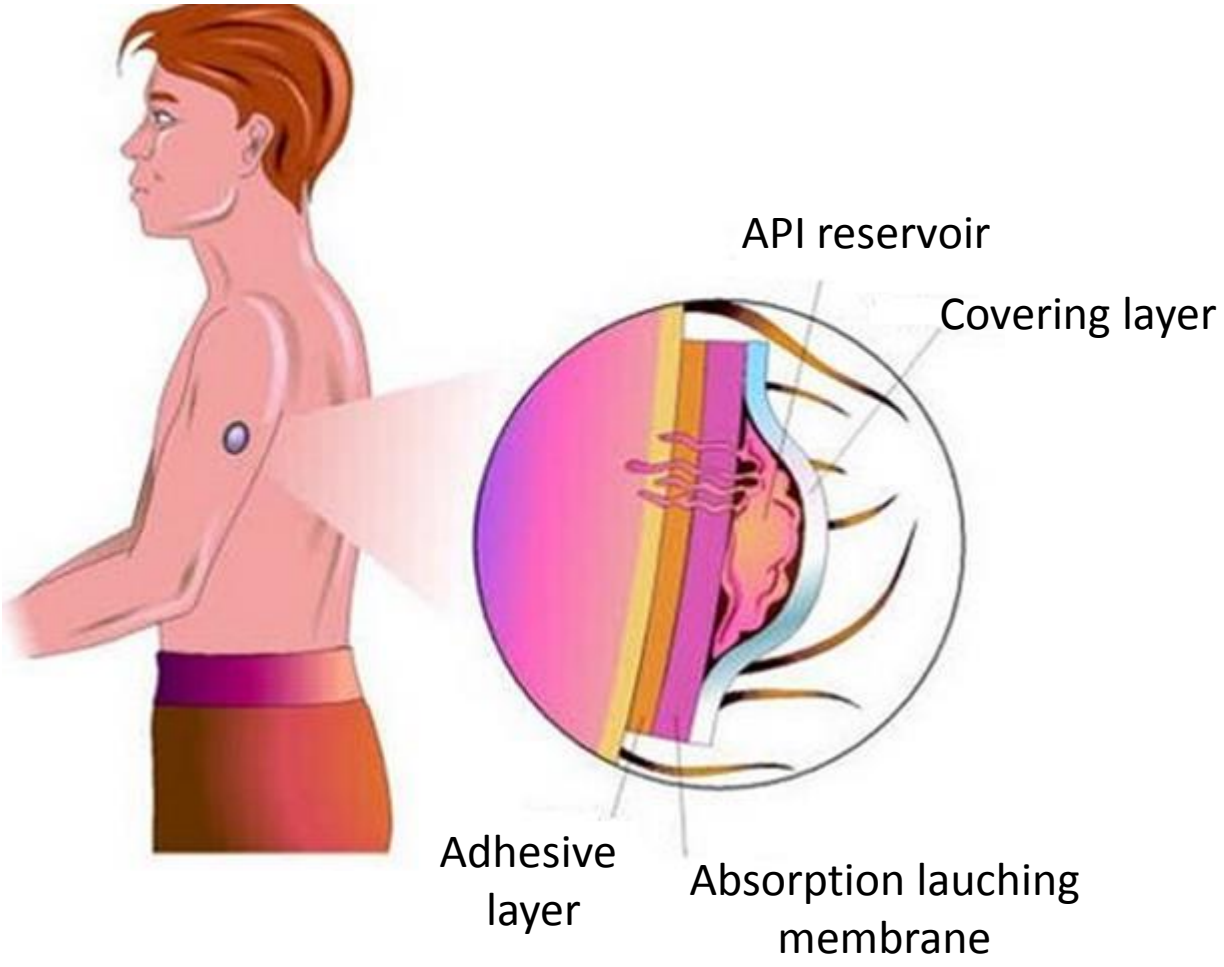
Transdermal administered preparation

patches

Transdermal drug delivery system

Patch (Emplastra transcutanea)

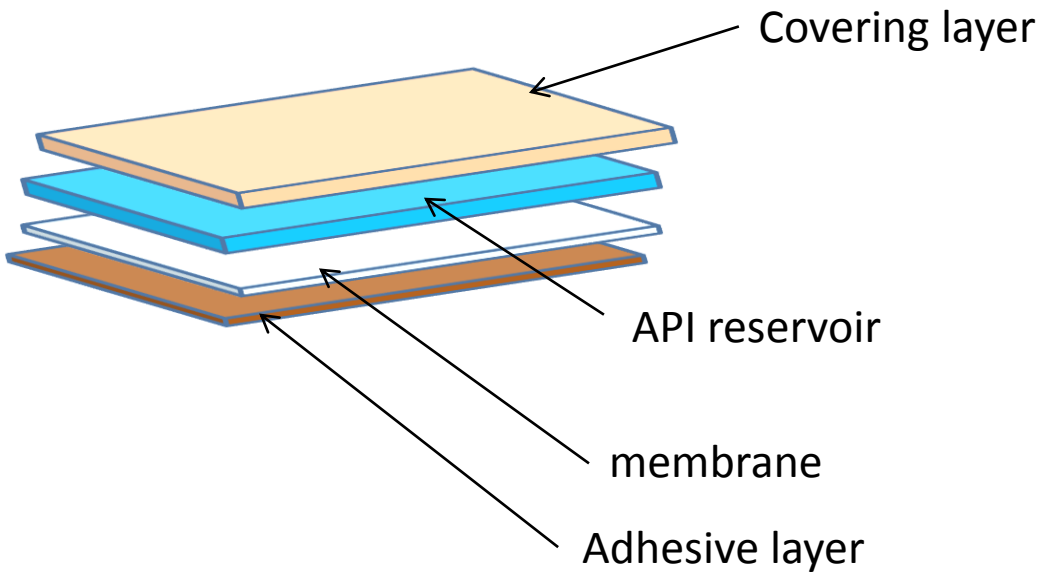
The transdermal patches are flexible, one or two API having preparation, which act through skin and designed in different sizes.



Transdermal drug delivery system

Controlling the absorption from transdermal patches

Membrane regulating liberation



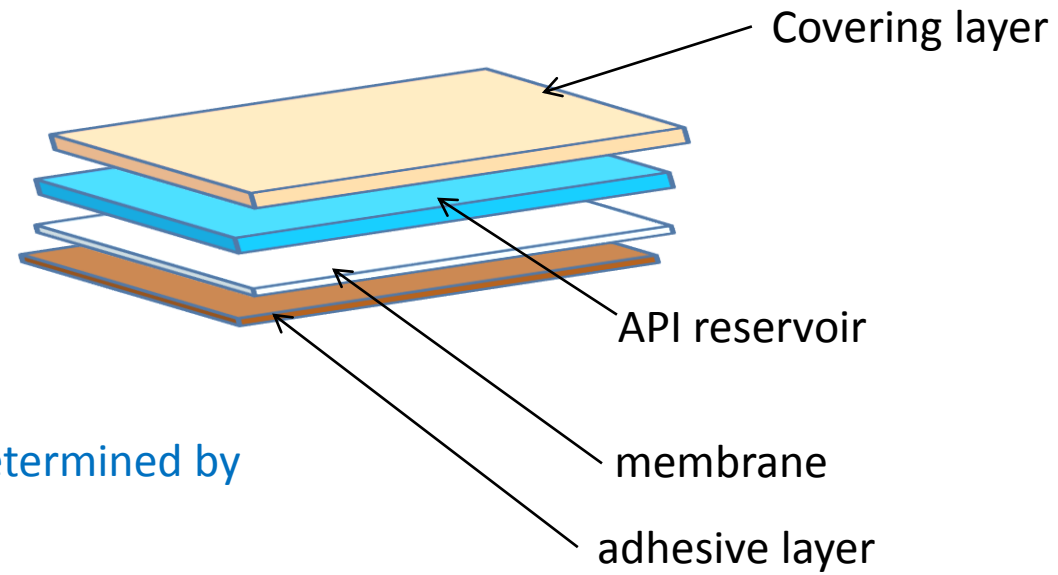
The API liberation is regulated by the membrane layer.
The protective film is a combination of aluminum and plastic film.

The API is suspended into the material of reservoir, which is usually some kind of polymer gel (e.g. silicon oil gelled with colloidal silizium -doxide). Frequently the adhesive layer consists API, to start the diffusion after sticking the patch onto the skin.

Transdermal drug delivery system

Controlling the absorption from transdermal patches

Membrane regulating liberation



1. membrane permeability is determined by

   a) type of membane
   b) thickness
   c) surface
   d) porosity

2. permeation assisting excipients

Transdermal drug delivery system

Controlling the absorption from transdermal patches

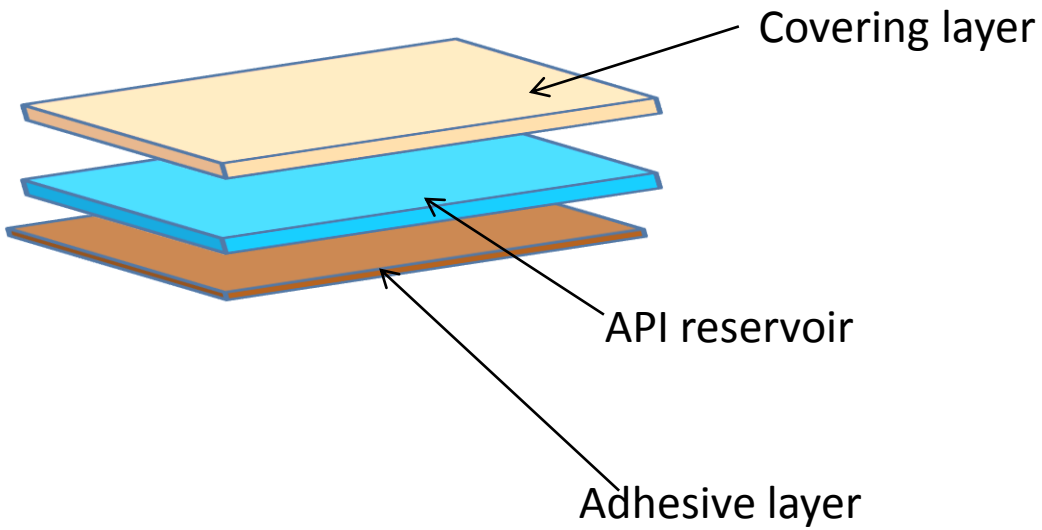
Membrane regulating liberation

The membrane can be such as **ethylene vinyl acetate copolymer**.

Transdermal drug delivery system

Controlling the absorption from transdermal patches

Adhesive layer regulated patches



The **diffusion** of API is **controlled by** individual structured **adhesive layer**.

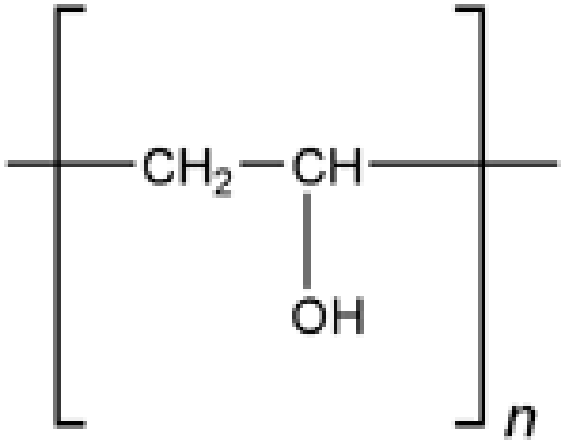
The **velocity** of API liberation is determined by the **composition**, **material**, **structure** of the reservoir.

Transdermal drug delivery system

Controlling the absorption from transdermal patches

Matrix regulated patches

The vehicle of reservoir is generally a **cross-linked polymer gel** (e.g. polivinyl-alcohol skeleton), which consists the API too.



Transdermal drug delivery system

Most frequent used substances

Substances	Molecular mass
scopolamine	305
nitroglycerin	227
nicotine	162
clonidine	230
fentanyl	336
estradiol	272
testosterone	288
lidocain	234

Transdermal drug delivery system

Nitroglycerin containing drug deliver systems

preparation	manufacturer / distributor	nitroglicerin content (mg)	Absorption surface (cm^2)	Rate of drug liberation (mg/hour)
Nitroderm TTS 5	Novartis	25	10	0,2
Nitroderm TTS 10	Novartis	50	20	0,4
Nitroderm TTS 15	Novartis	75	30	0,6

In the name of Nitroderm TTS 5, TTS 10 and TTS 15 (Novartis) preparations, the numbers are the liberated nitroglycerin quantity within 24 hours in mgs.

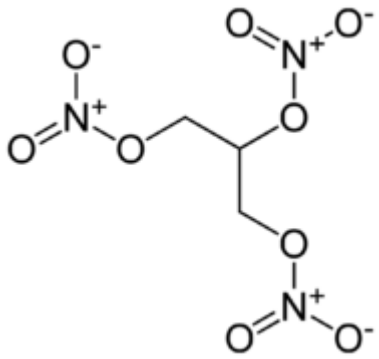
Transdermal drug delivery system

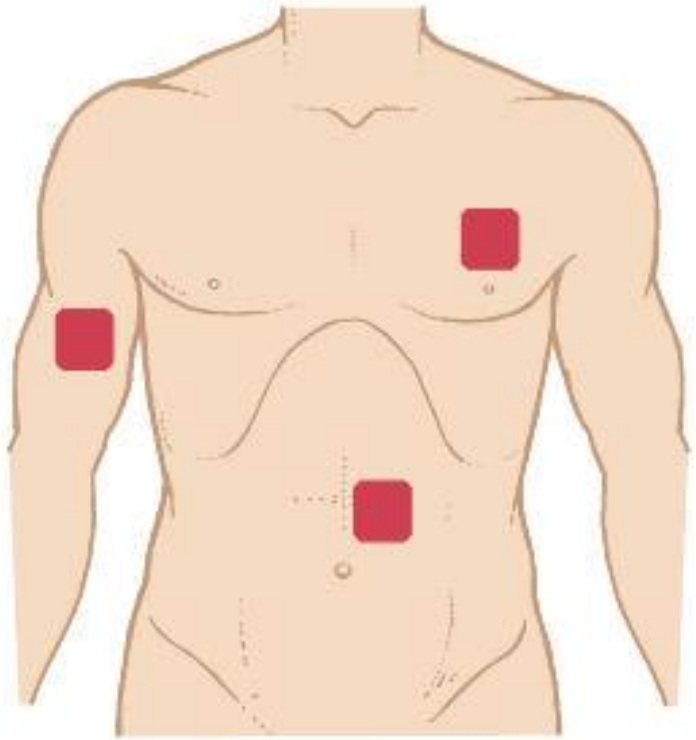
Nitroglycerin containing drug deliver systems

Application mode	Drug deliver system	Beginning of effect	Legth of effect
perlingval	In mouth disintegrating tablets	2-4 minutes	0,5-1 hour
sublingval	tablet, spray	1-1,5 minutes	0,5 hour
buccal	Prolonged drug delivery tablets	2-3 minutes	5 hour
intravenous	solution	immediately	some minutes
transdermal	Transdermal patch	40-60 minutes	16-24 hour

Transdermal drug delivery system

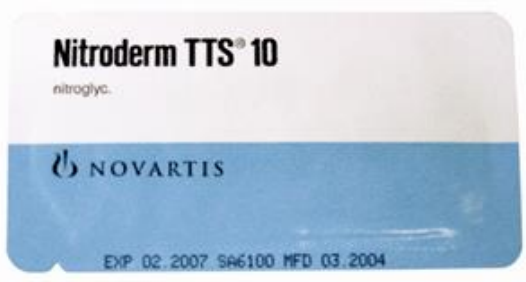
Possible application sites of nitroglycerin cointaing patches

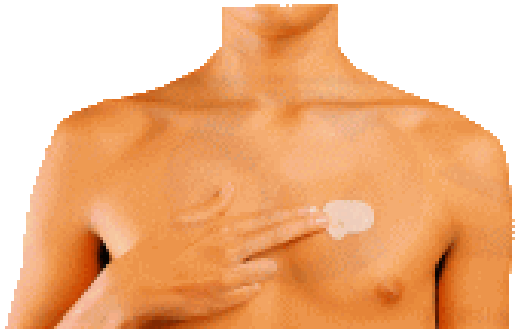




Transdermal drug delivery system

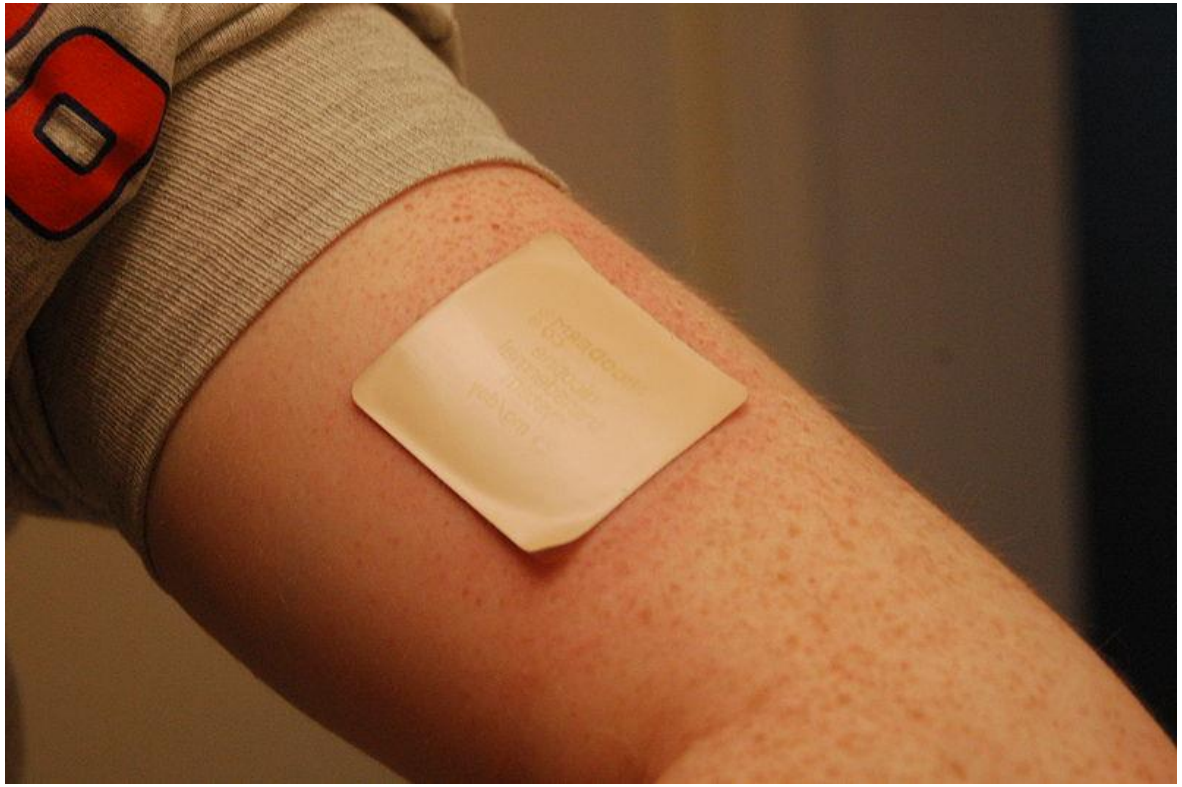
Nitroglycerin cointaing patch





Transdermal drug delivery system

Nicotine cointaing patch



NICOTINELL TTS 10 transdermal patch
API: nicotine

Transdermal administered preparation

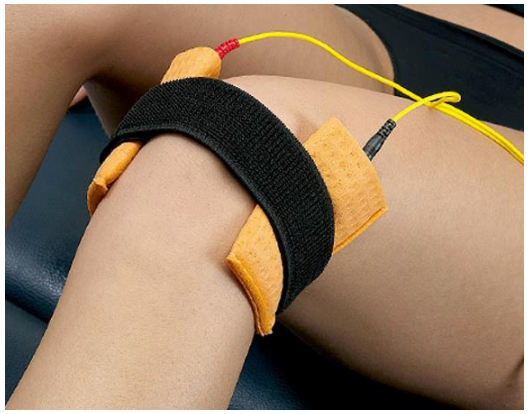
Iontophoresis

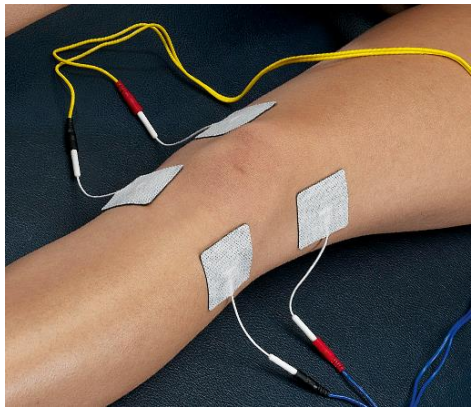
Transdermal drug delivery system

Iontophoresis

Penetration of API molecules can be enhanced:

- in case of **charged molecules** by **electrophoresis**,
- in case of **small or uncharged molecules**, the movement of the mobile ions (such as sodium ion) result consequential water movement, thus by **electroosmosis**.

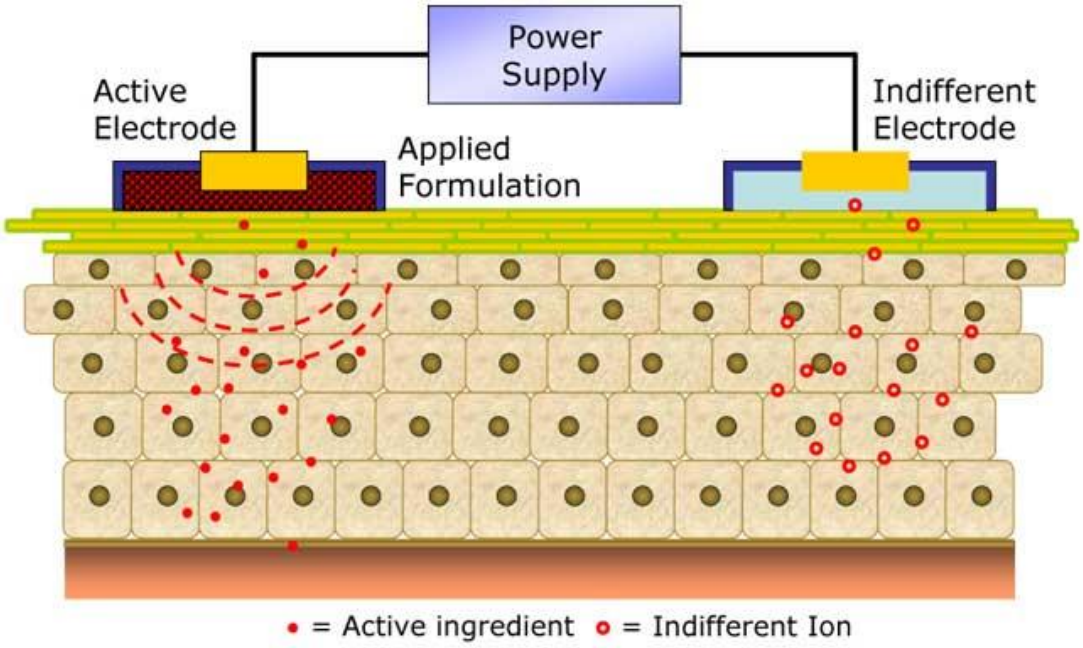




Iontophoresis

In practice on of the electrode is put in the skin surface onto the solution or gel of API, while the other is taken on the other side of body. In this electro-impulse effected power field move the molecules into the tissues.

This technology is recommended in case of arthritis chronic degenerative and inflammatory joint or spinal diseases.



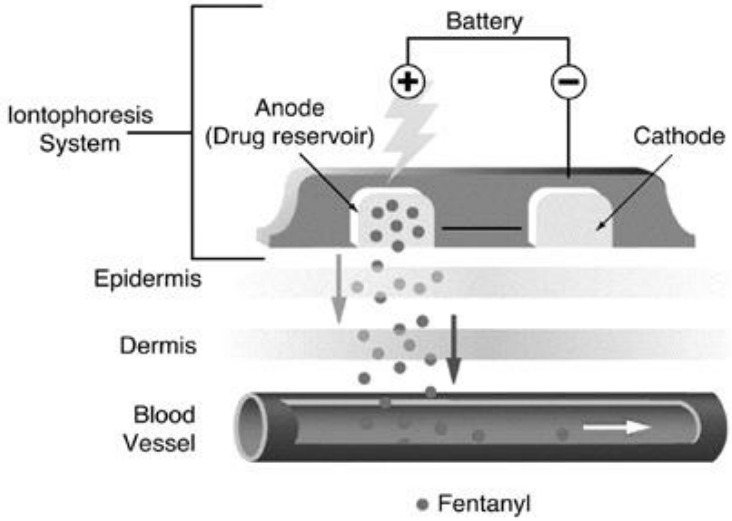
Transdermal drug delivery system

Iontophoretic Transdermal System, ITS

With this device the patient can activate the dosage as required.

The fentanyl containing *IONSYS® (Janssen-Cilag)* preparation is for relieving the acute, postoperative middle or intense pain if it is indicate during hospitalization.

At the beginning the dosage effected electricity programmed, determined quantity of fentanyl goes from the API reservoir to the systemic circulation.



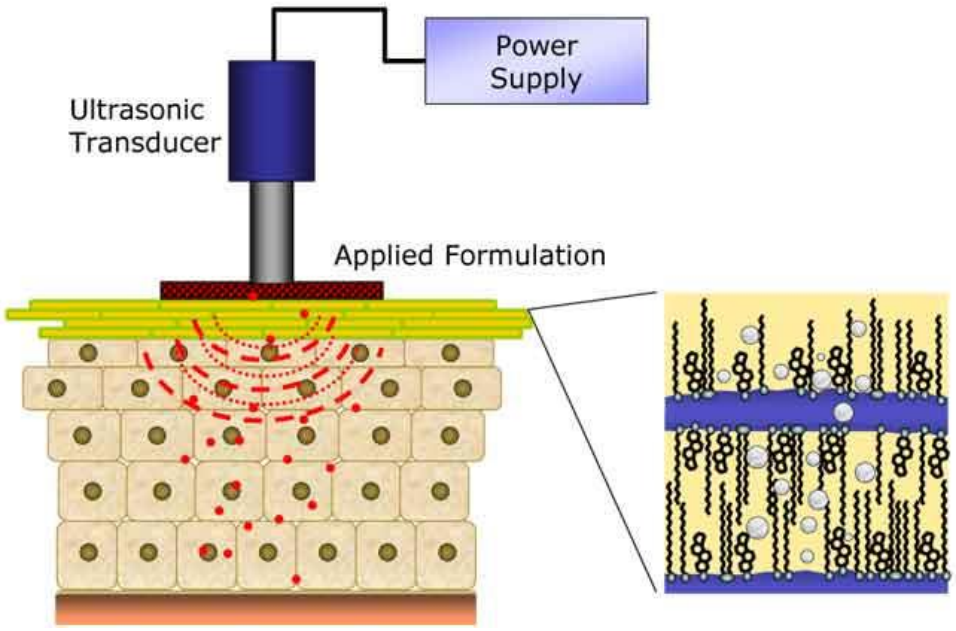
Transdermal administered preparation

ultrasound

Transdermal drug delivery system

Ultrasound (phonophoresis)

For the ultrasound the intercellular structure of stratum corneum will be permeable (fat layer), which can be assisted with heating.

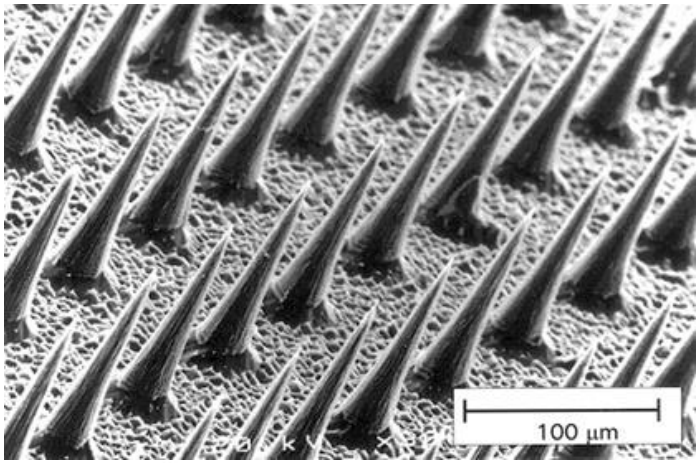


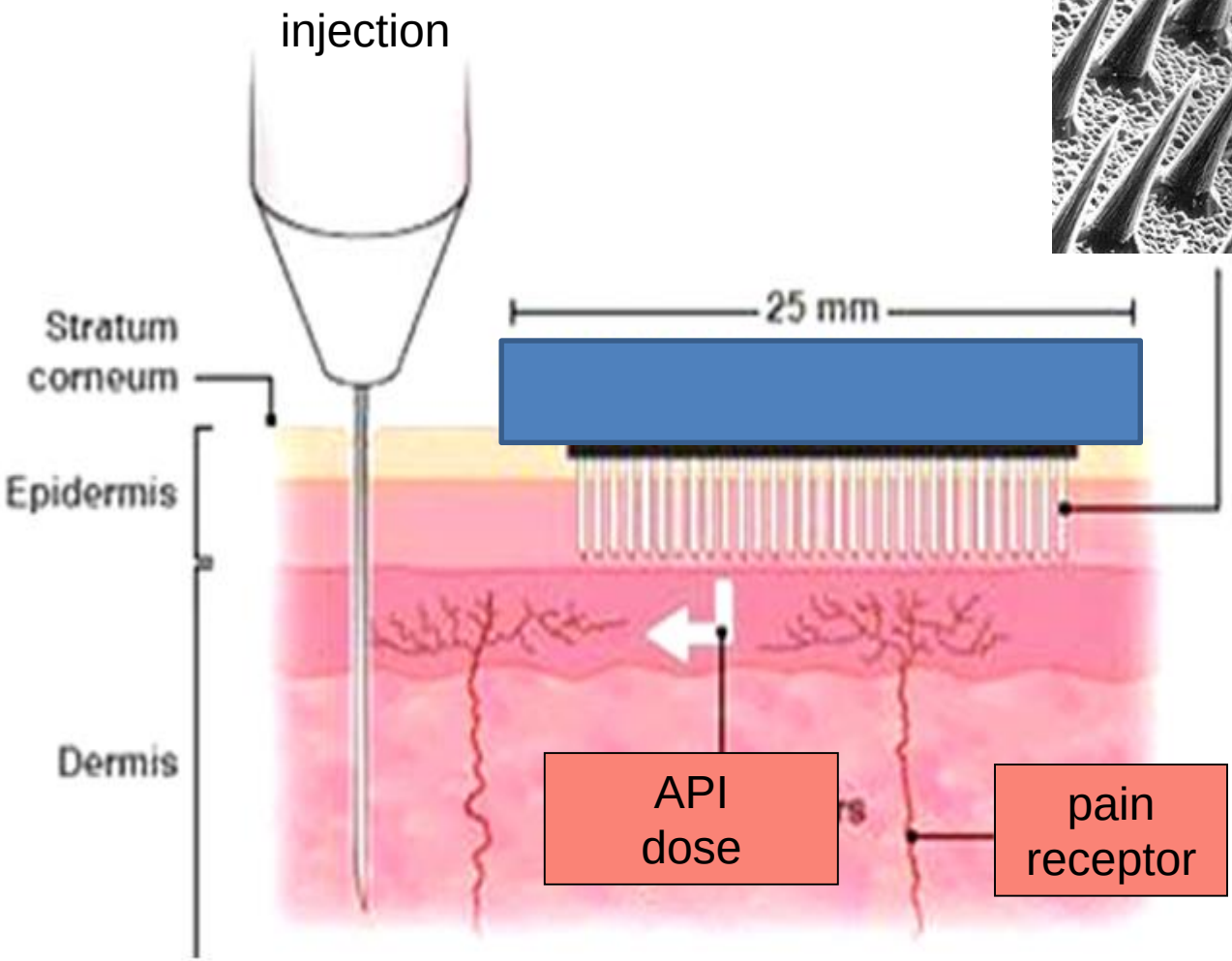
Transdermal administered systems

microneedles

Transdermal drug delivery system

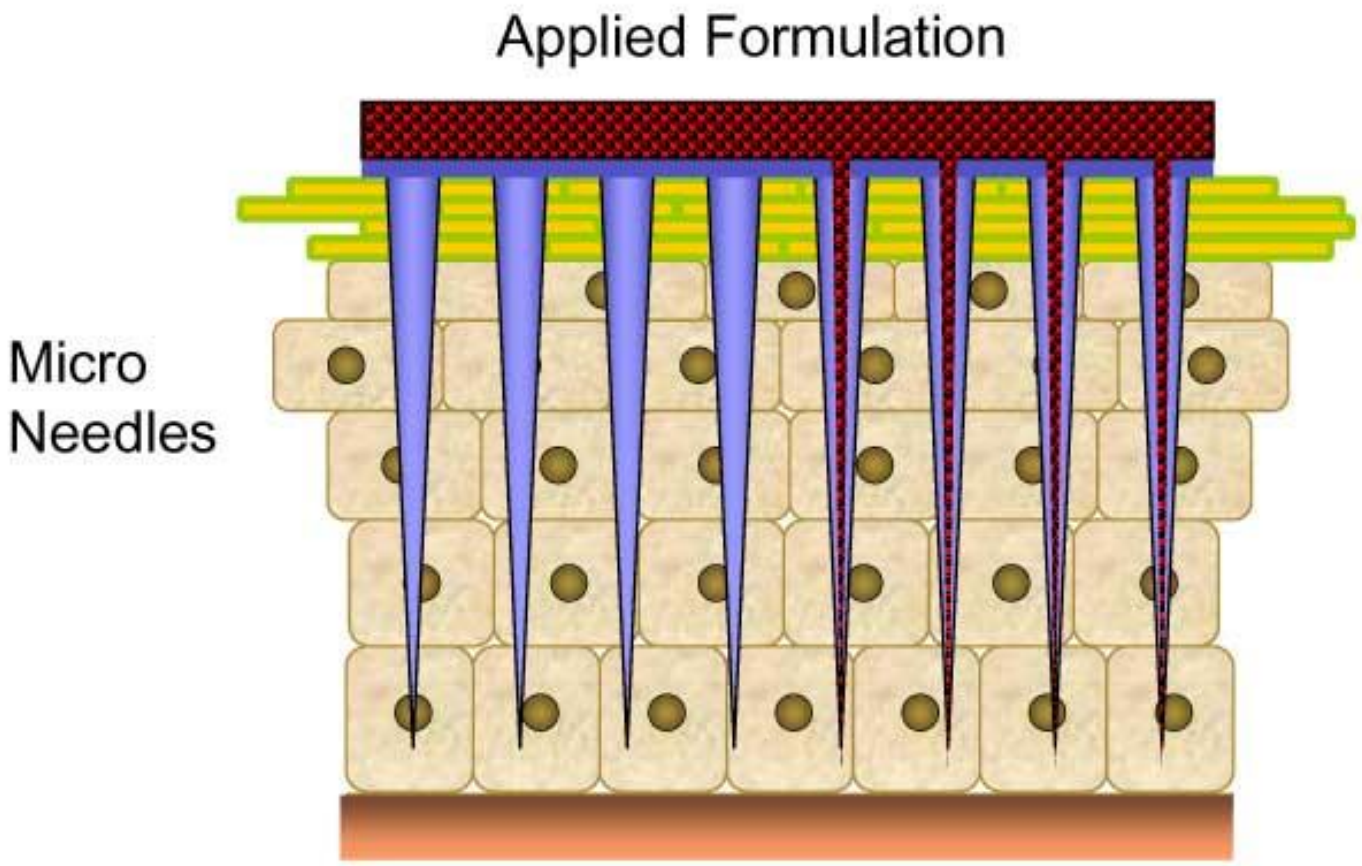
Microneedle-type transdermal delivery system





Transdermal drug delivery system

Microneedle-type transdermal delivery system



Transdermal administered preparation

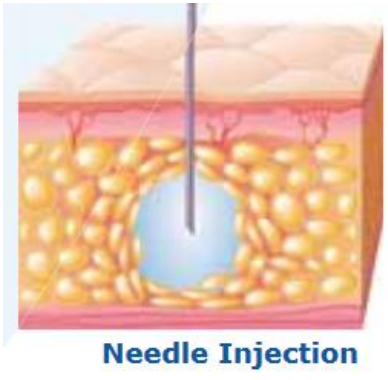
jet injectors

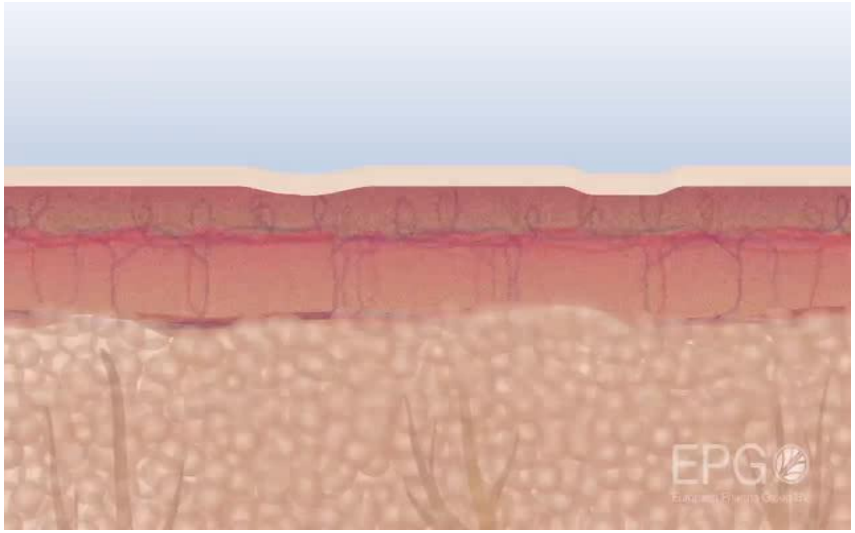
Transdermal drug delivery system

Jet injectors

The jet injectors achieve to inject the API with high pressure (some kind of gas, or air) through skin.

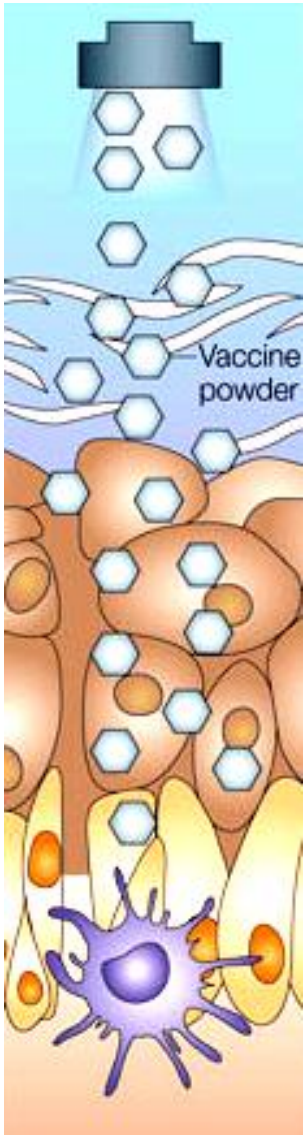
These are also capable for vaccination.

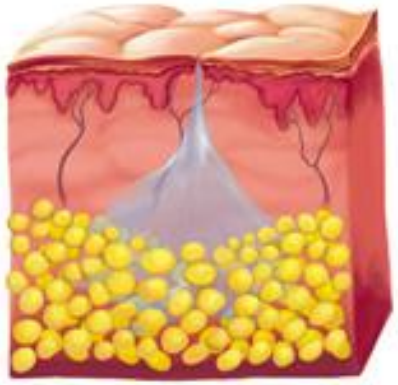




Transdermal drug delivery system

Jet injectors

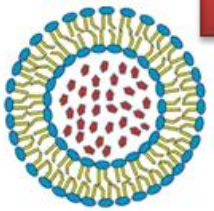


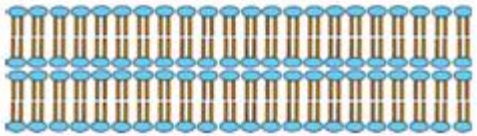


Transdermal administered preparation

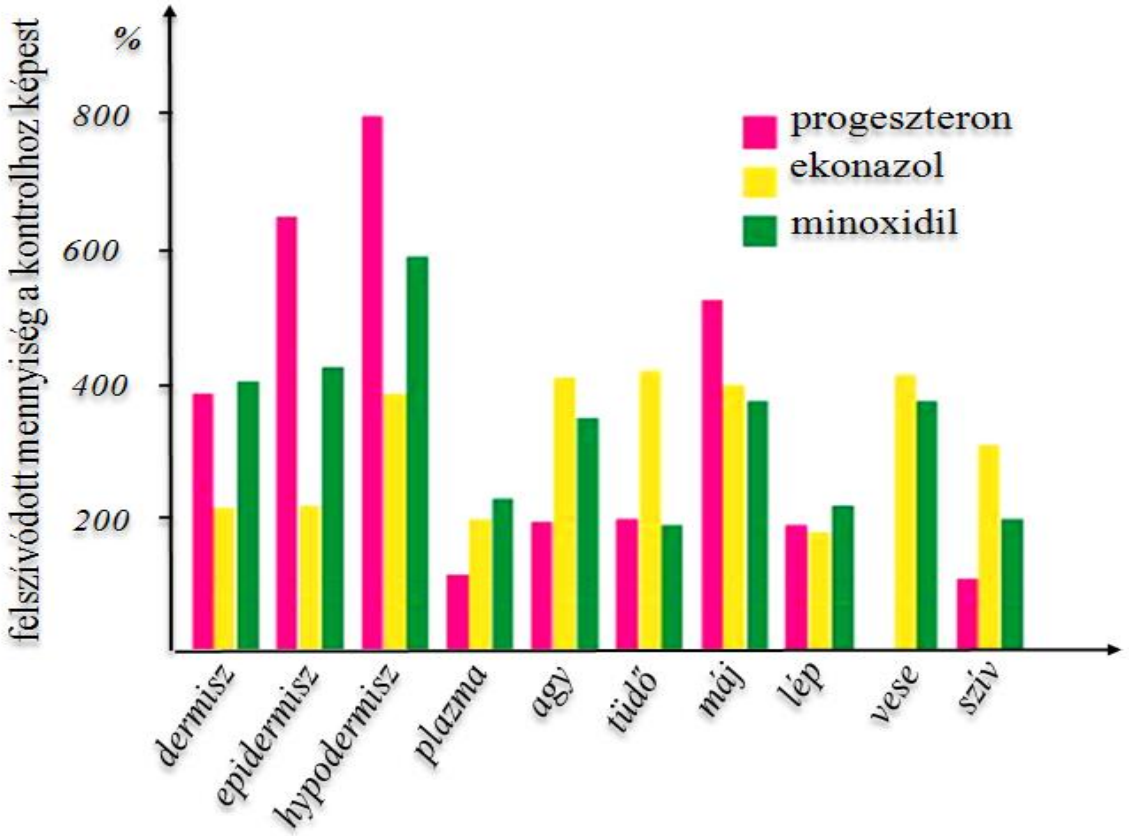
Nanostructures

Liposomes





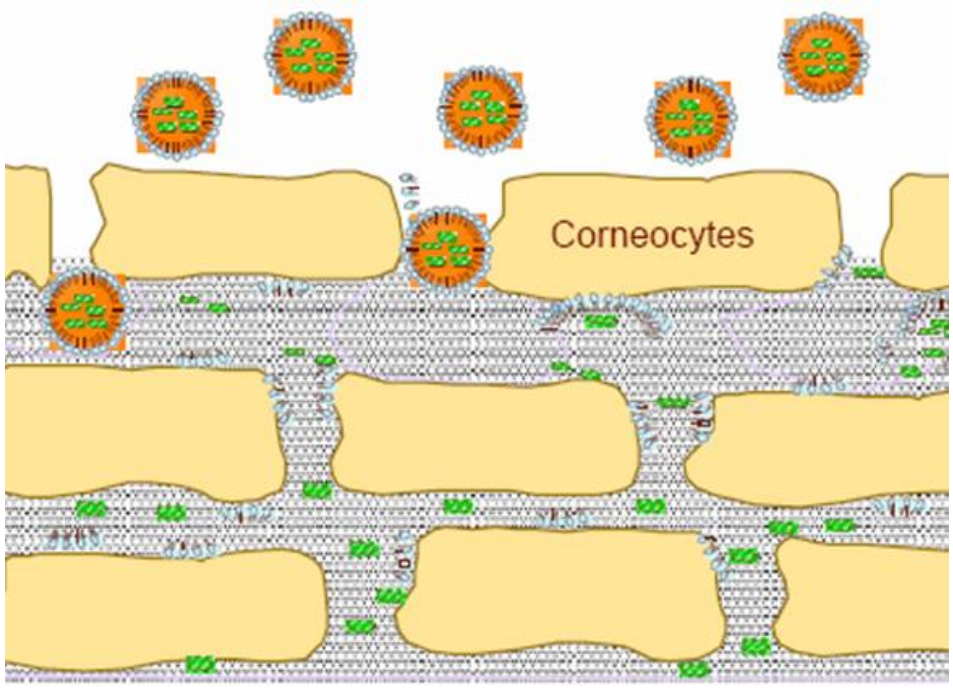
The liposomes has got very similar structure to living cells (phospholipid bilayer) and can transfer the APIs into deeper layers.



Distribution of API after additon in liposome form

Nanoemulsion

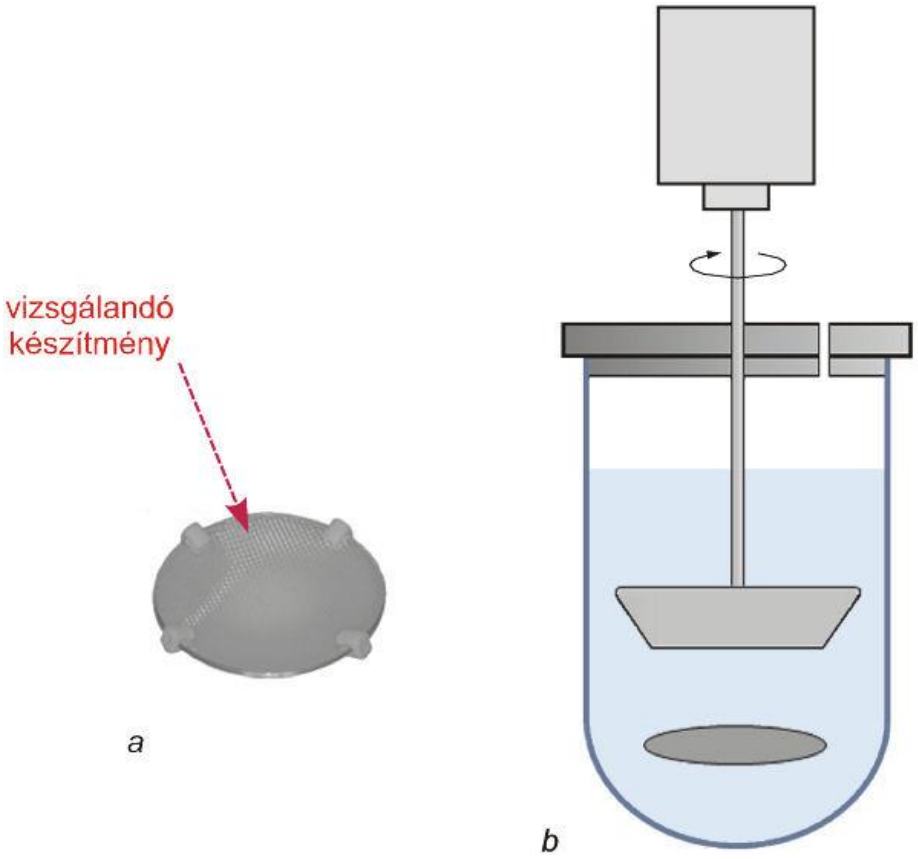
Nanoemulsion is a system – such as a mix of oil and water – in which the liquid drops (oil) are nano sized and surrounded by the other liquid (water). Their surface tension is high, hence when they contact with unicellular organisms (like bacteria, fungus), they can eliminate them by breaking their cell wall.



Examination of transdermal administered preparation

Examination of preparations

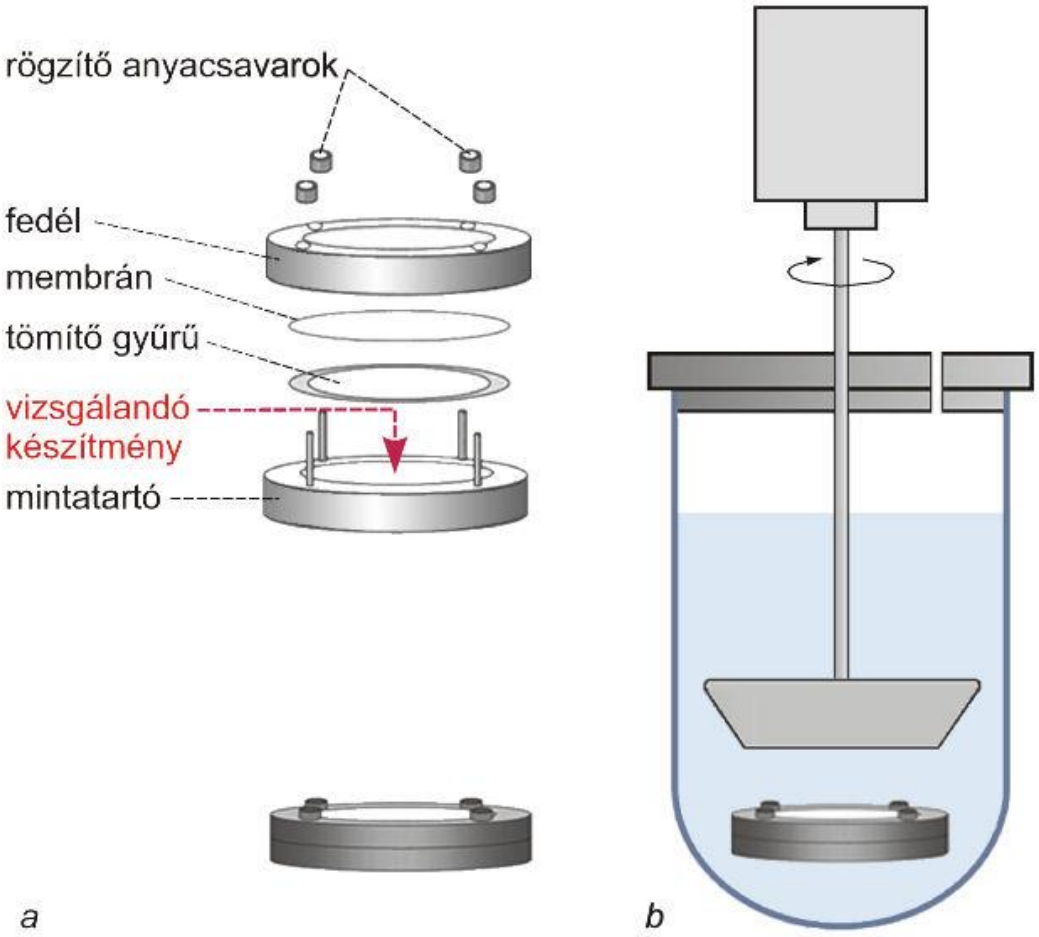
Examination of transdermal patches is performed by stainless steel disc assembly method.



a. Insertion the examined preparation onto disc
b. Assembled dissolution test

Examination of preparations

Examination of transdermal patches with extraction cell



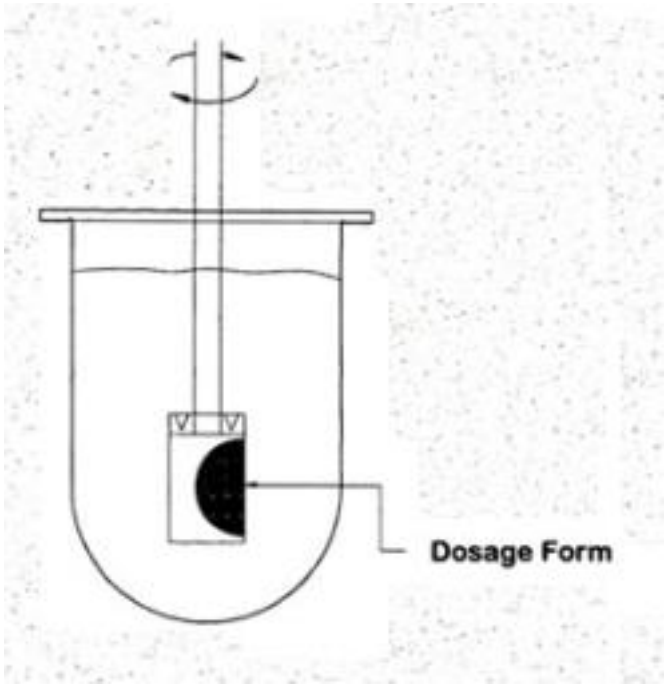
a. Insertion the examined preparation into disc
b. Assembled dissolution test

Examination of transdermal patches with **rotational cylinder**

- The rotary paddle device is also applicable in this case.
- The paddle is replaced by a cylinder.
- The patch is applied to the adhesive surface on a suitable inert material porous membrane.
- The membrane on each side should be at least 1 cm higher than the patch.

Examination of preparations

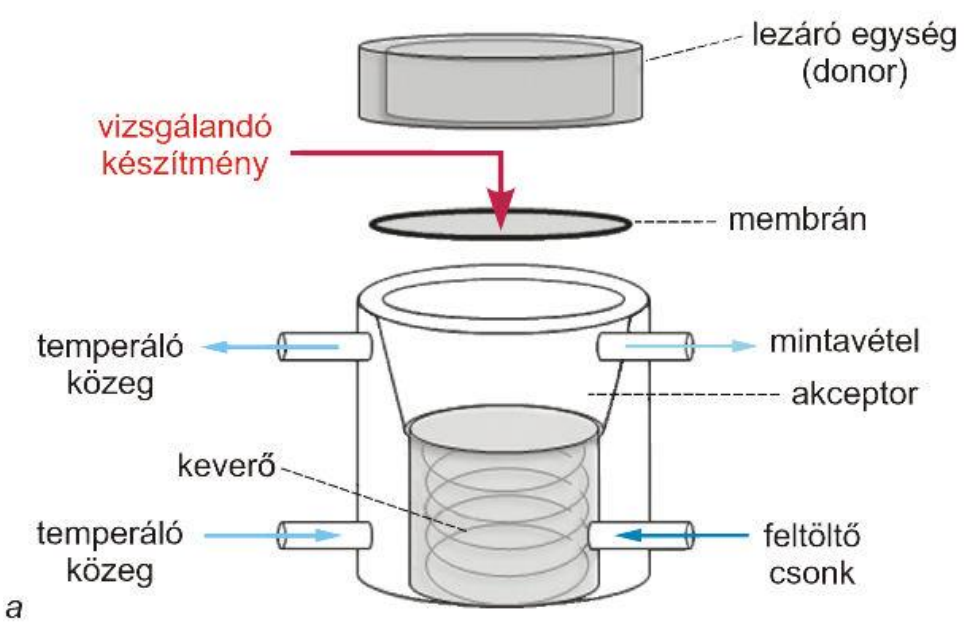
Examination of transdermal patches with **rotational cylinder**



USP Apparatus 6

Examination of preparations

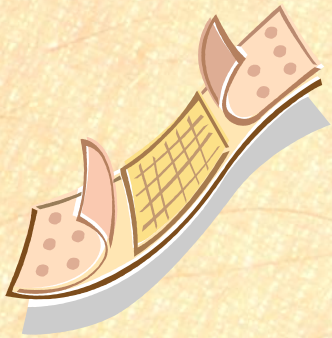
Franz diffusion cell



Construction of examining instrument

Photo of the cell

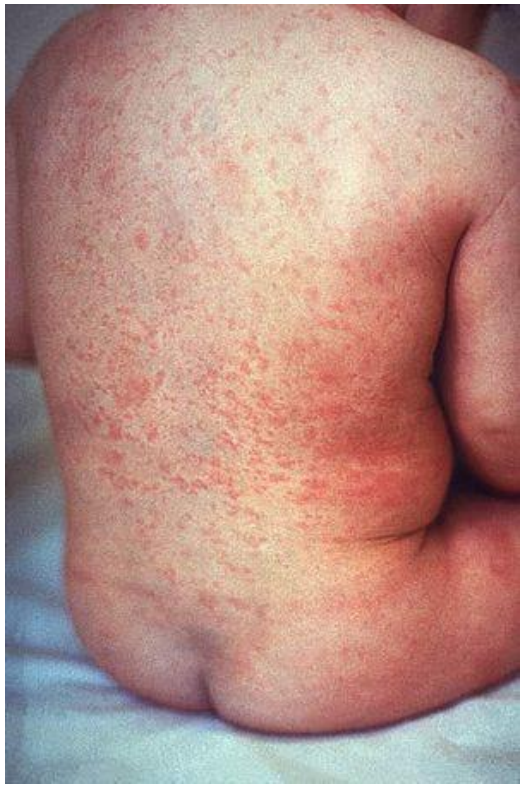
More common skin disorders

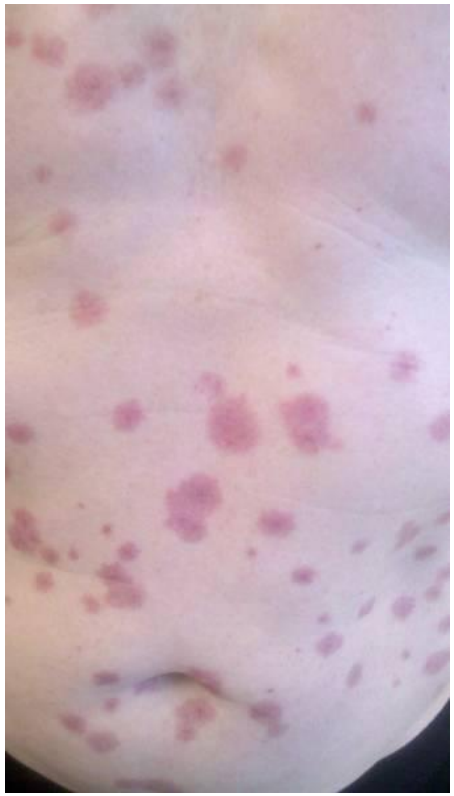


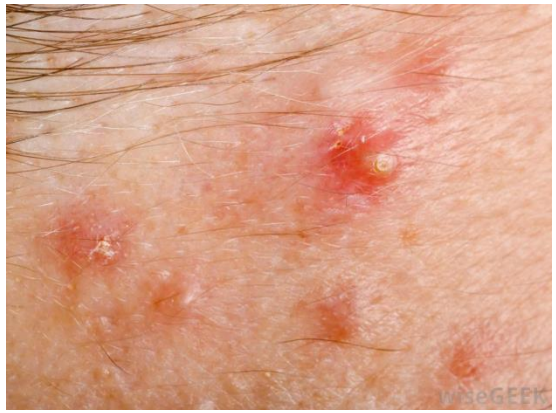
Images that can calm the peace of mind are coming!

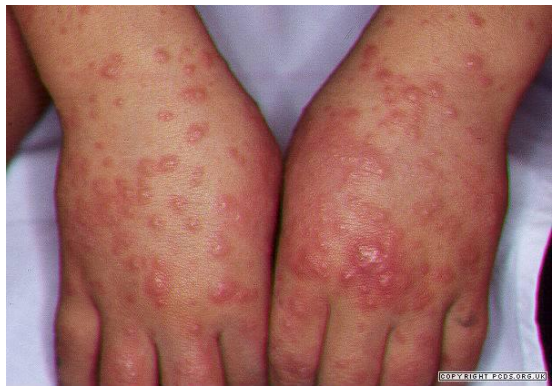
More common skin disorders

1) Skin rash *(exanthema)*



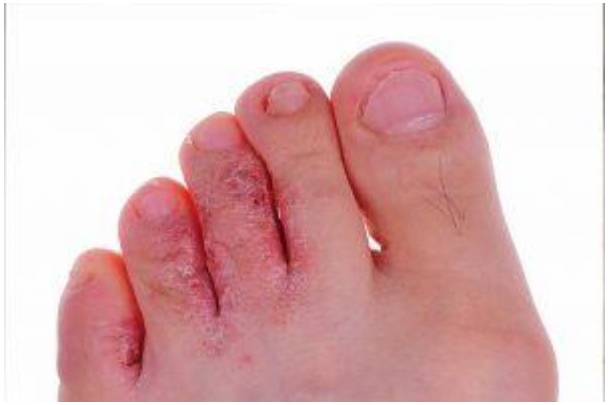


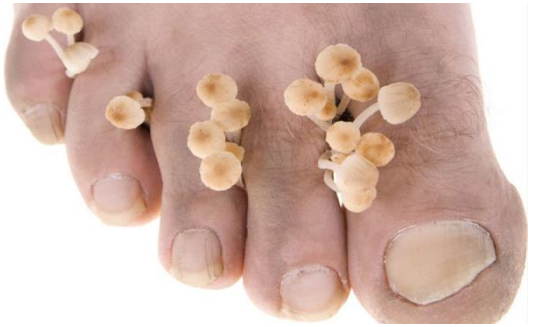


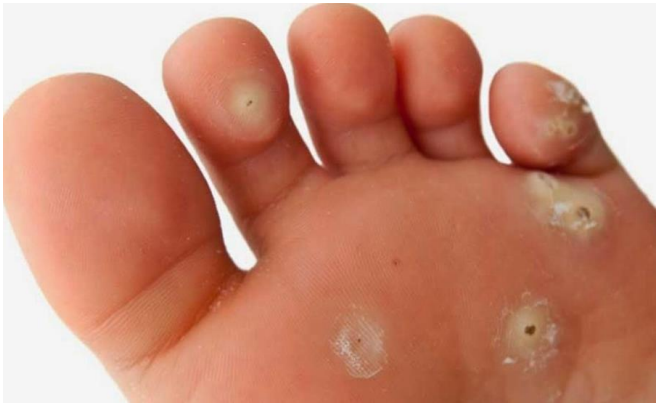


More common skin disorders

2) Dermatophytoses *(dermatomicosis)*

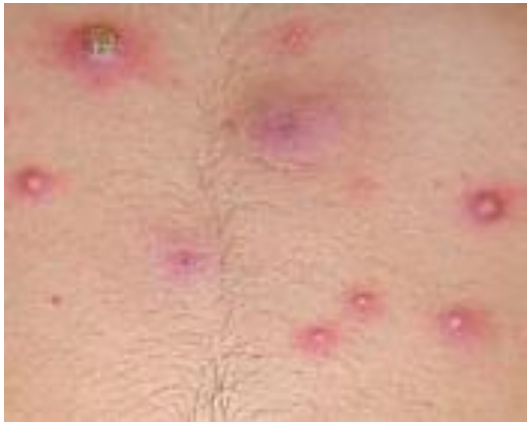


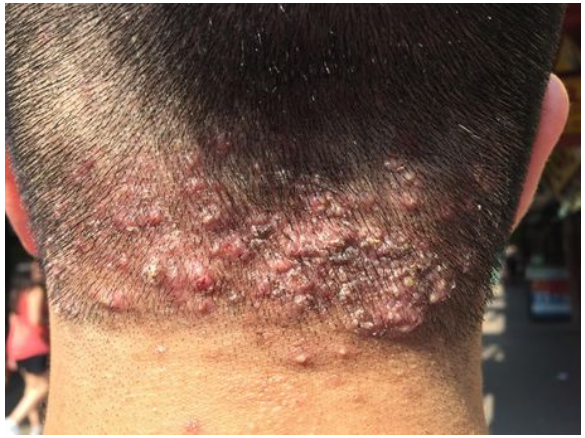


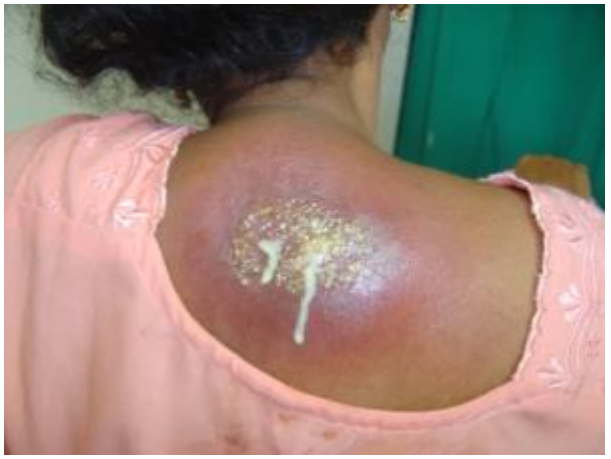


More common skin disorders

3) Bacterial infections *(eg. carbunculus, furunculosis)*



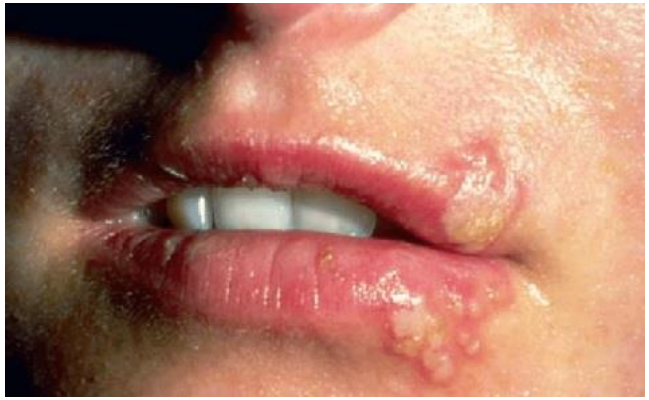


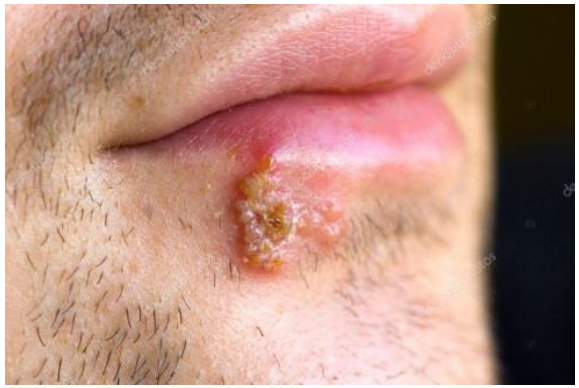


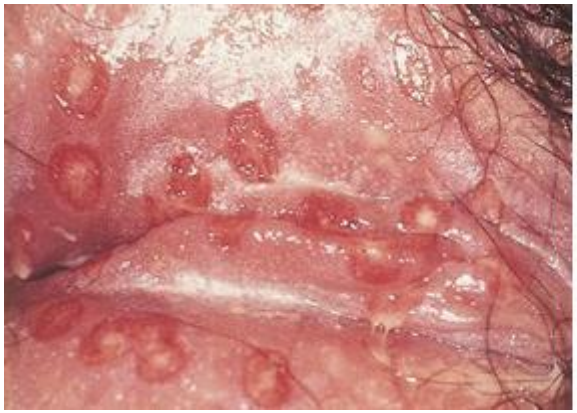
More common skin disorders

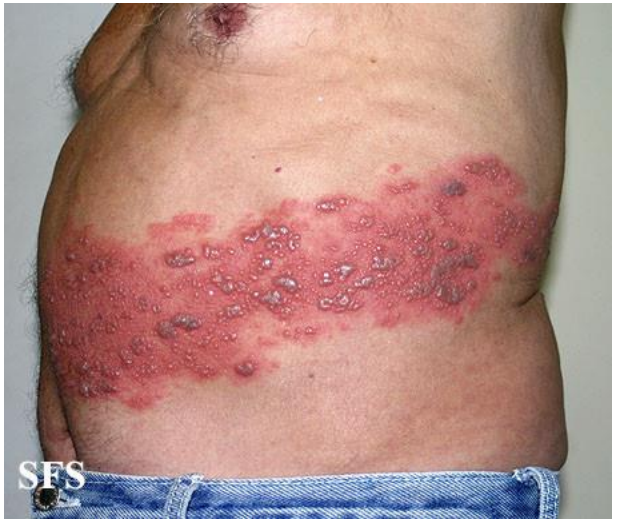
4) Virus-related infections *(eg. herpes simplex)*

- Herpes labialis
- Herpes genitalis
- Herpes zoster



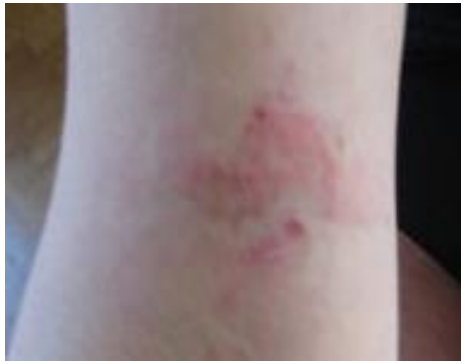


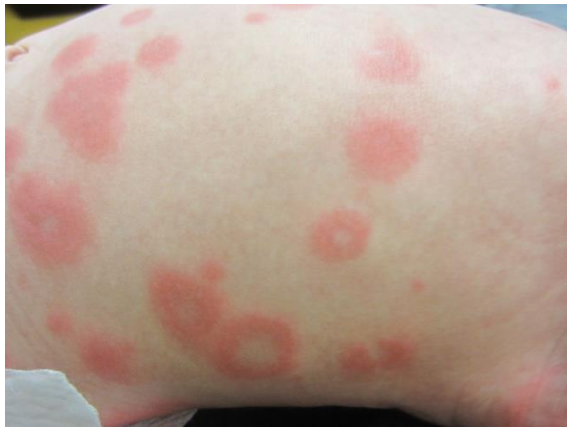


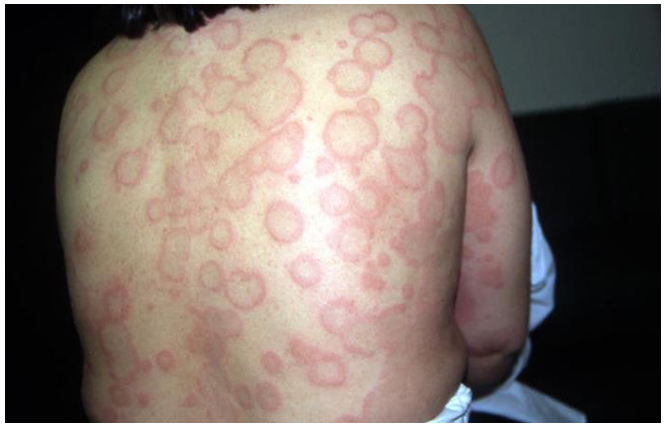


More common skin disorders

5) Allergy *(urticaria)*

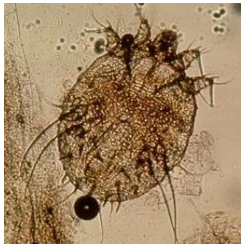


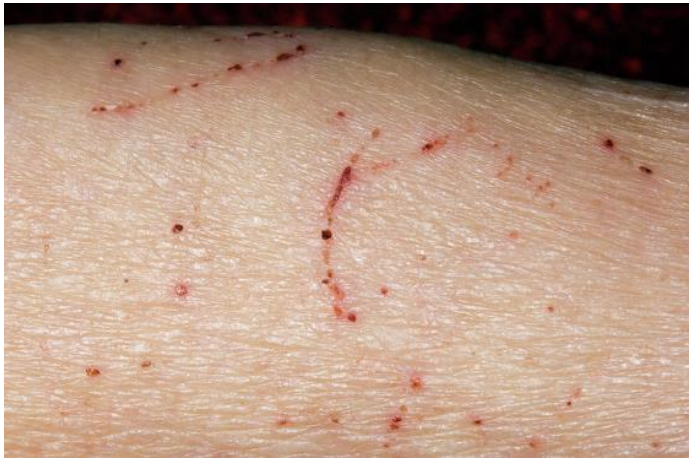




More common skin disorders

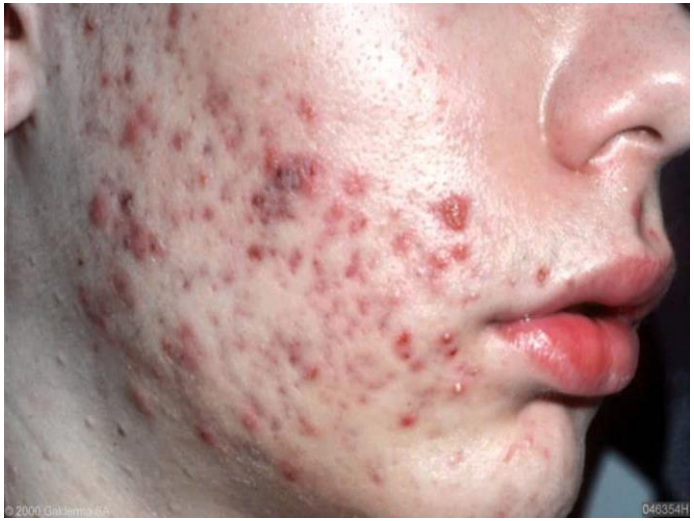
6) Parasites *(eg. scabies)*

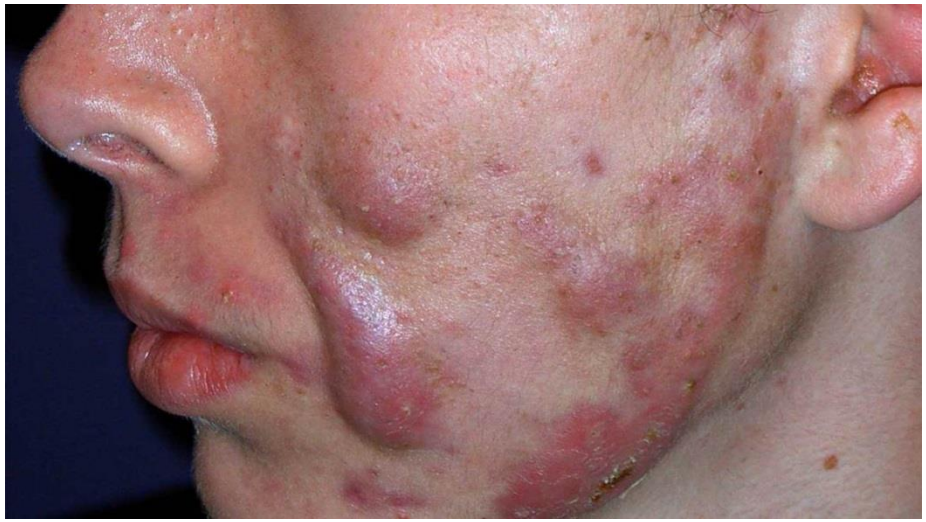




More common skin disorders

7) Dysfunction of the skin glands *(eg acne, hair follicles)*

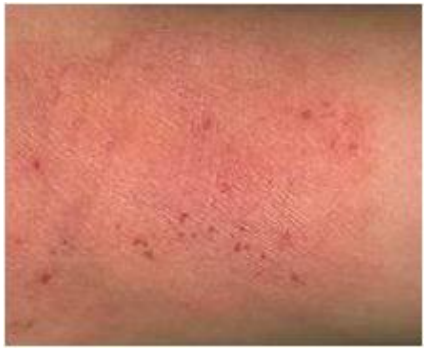


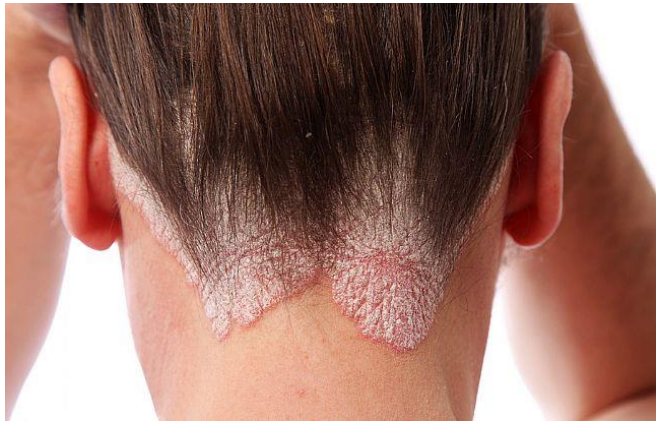


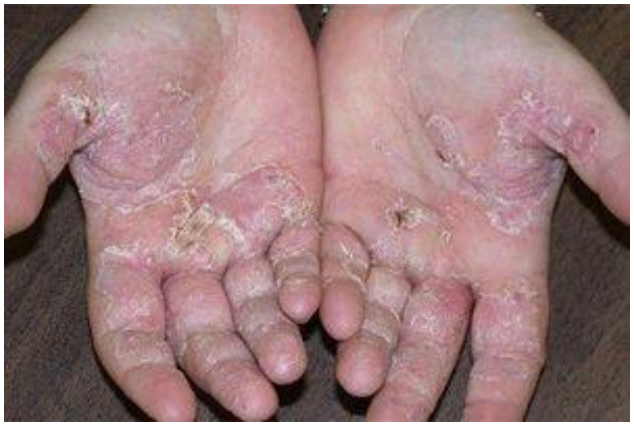
Not contagious!

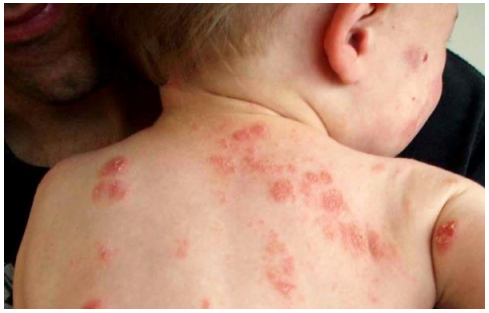
More common skin disorders

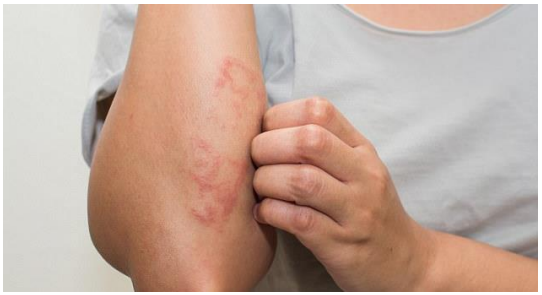
8) Eczema *(dermatitis)*,

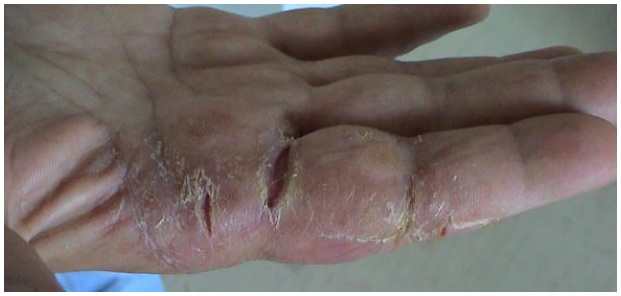






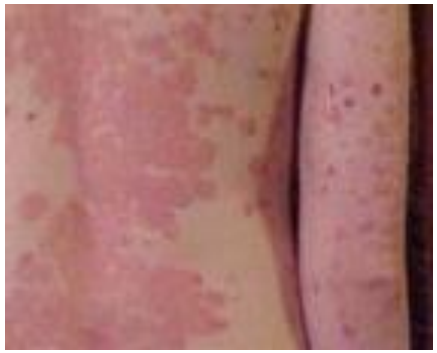


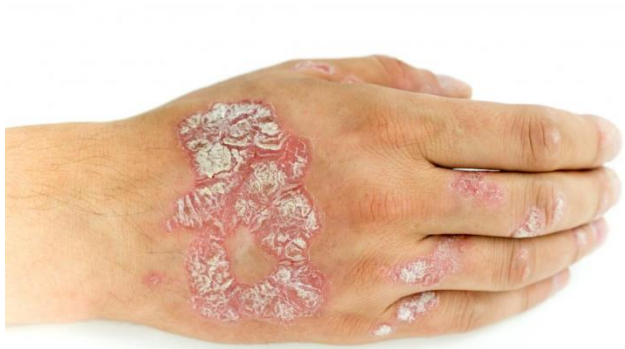


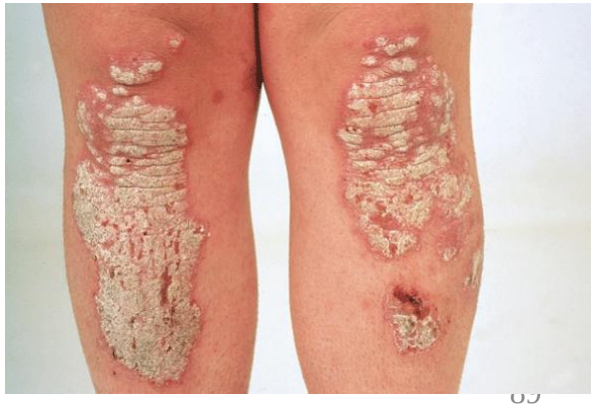


More common skin disorders

9) Psoriasis

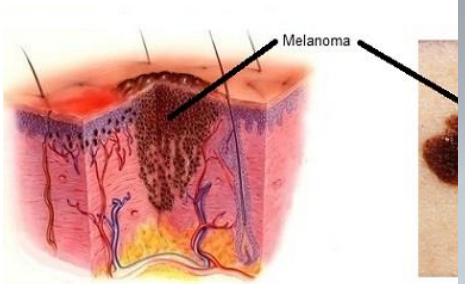


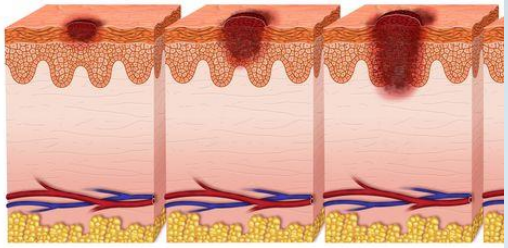


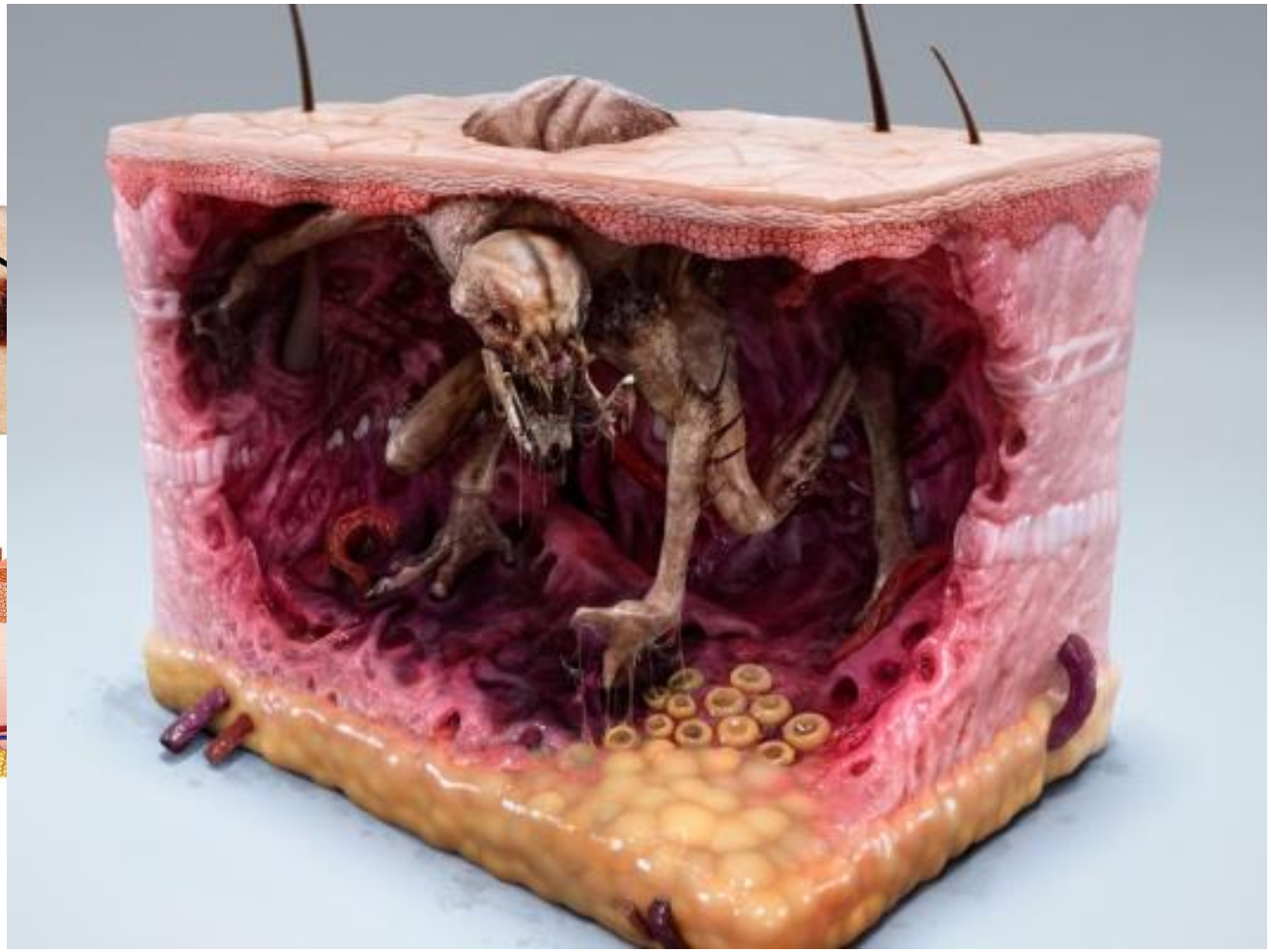


More common skin disorders

10) Skin cancer *(melanoma)*







Thank you for your attention!