Enhacers of transdermal, buccal, and intestinal drug absorption

Buccal, intestinal and skin barriers: through them, a drug can be administered into blood circulation

Comparison of structure of the skin, oral cavity mucosa and small intestine mucosa

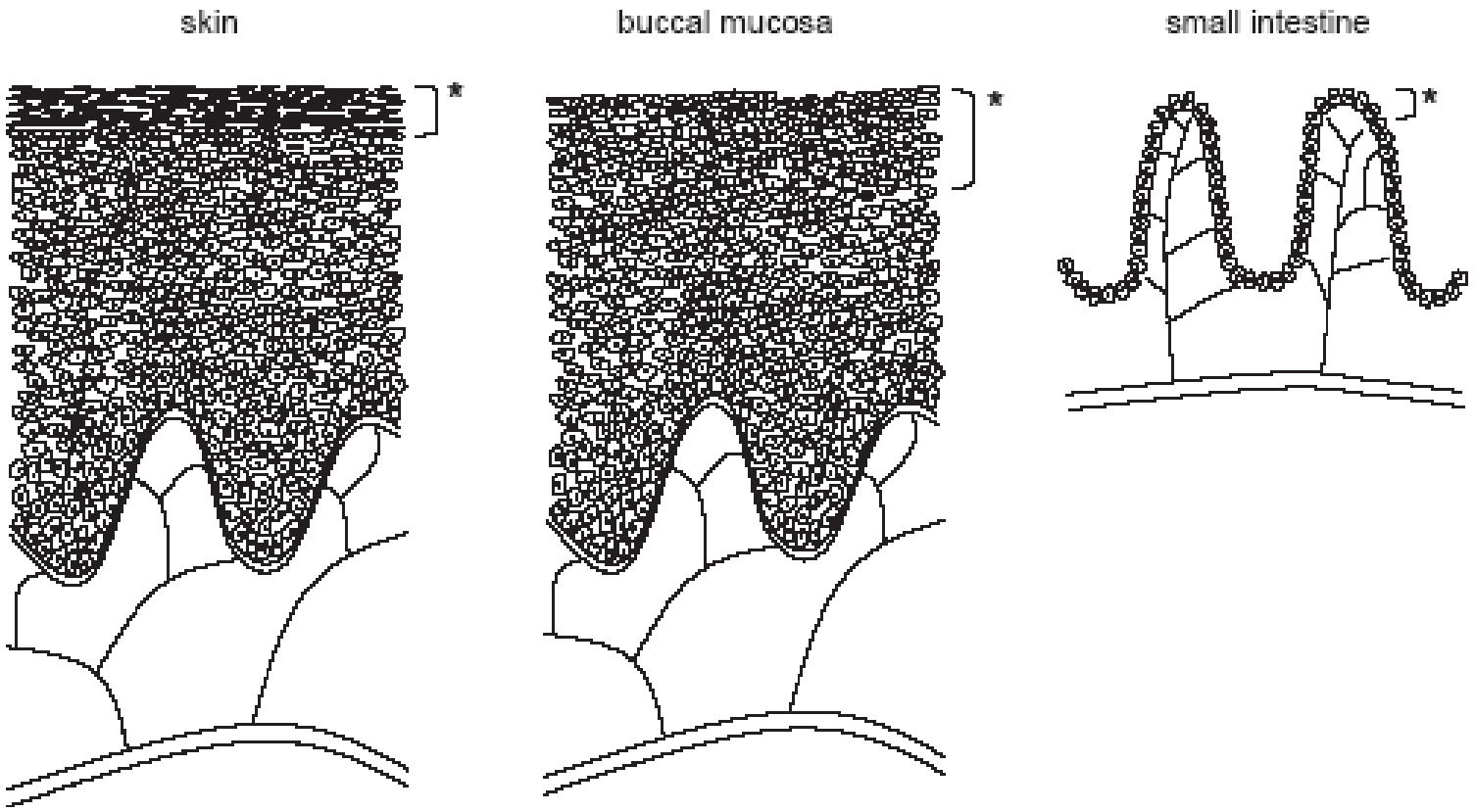
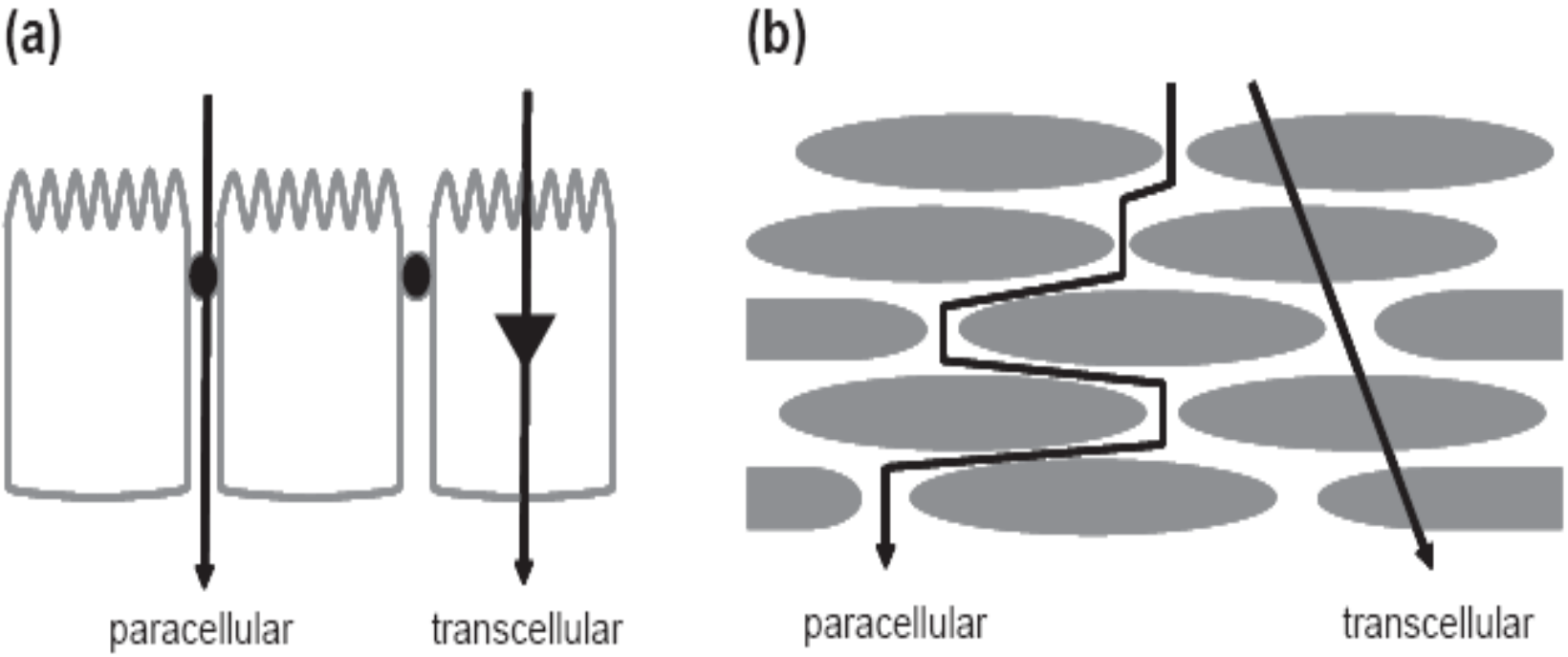


Fig. 1. A structural comparison of the skin, buccal mucosa, and small intestine. The skin and buccal mucosa are covered by a stratified squamous epithelium, whereas the surface of the small intestine consists of a simple columnar epithelium. The region associated with the barrier properties of each tissue is highlighted by the asterisk. This diagram is not drawn to scale.

Comparison of structure of the skin, oral cavity mucosa and small intestine mucosa

- the skin and buccal mucosa are covered by a stratified squamous epithelium, whereas the surface of the small intestine consists of a simple columnar epithelium
- oral cavity mucosa is keratinized in some places whereas the skin everywhere (*stratum corneum*)*;* permeation through the keratinized layer demands increased lipophilicity

Transport ways of d. through the buccal mucosa in comparison with the small intestine mucosa

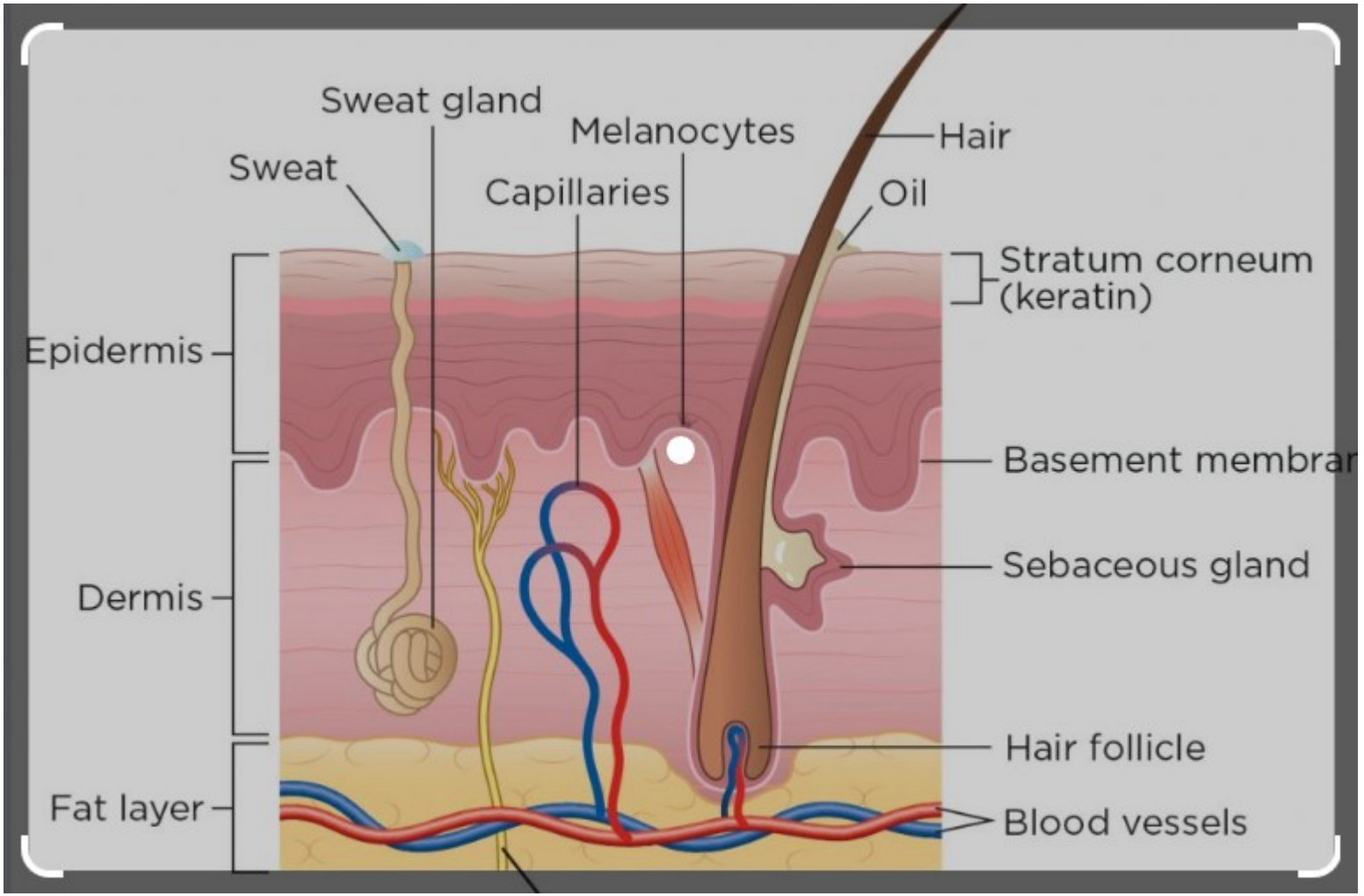


small intestine

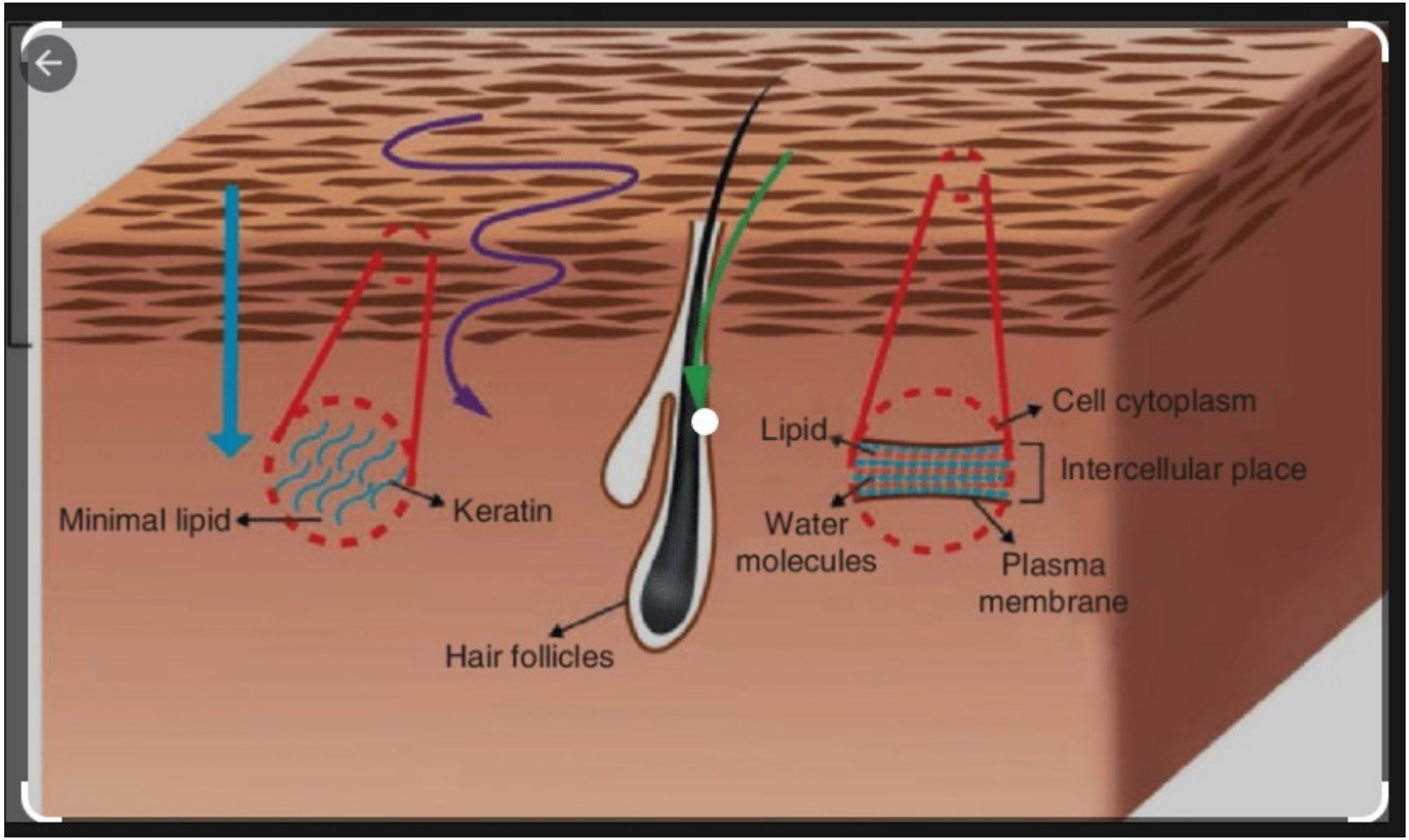
buccal mucosa (oral cavity)

•comparatively hydrophilic compounds penetrate through the paracellular way whereas hydrophobic ones prefer transcellular way; increased lipophilicity is needed for penetration through the buccal mucosa

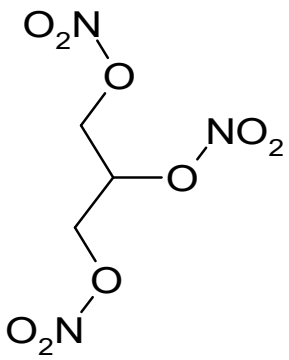
Cross-section through the skin



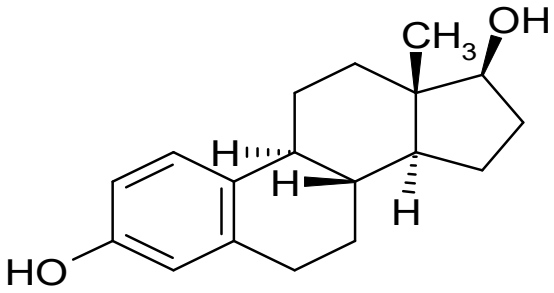
Transcellular & paracellular ways of permeation of molecules through the skin



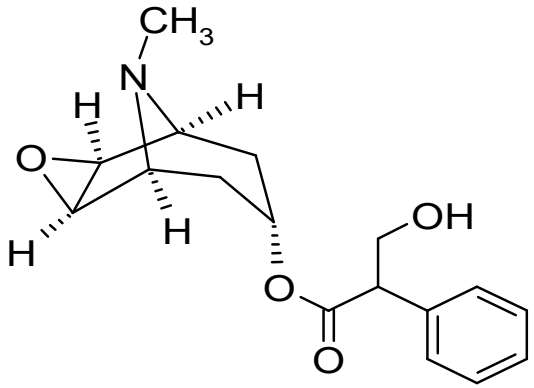
•only limited number of compounds can permeate through the skin into the blood circulation spontaneously, in most they are molecules of higher lipophilicity, such as



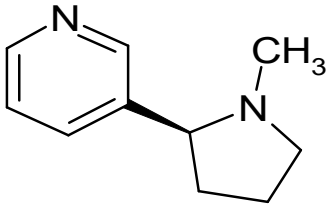
glycerol trinitrate
log P = 1.62
- also buccaly
Nitroglycerin-Slovakofarma orm tbl buc



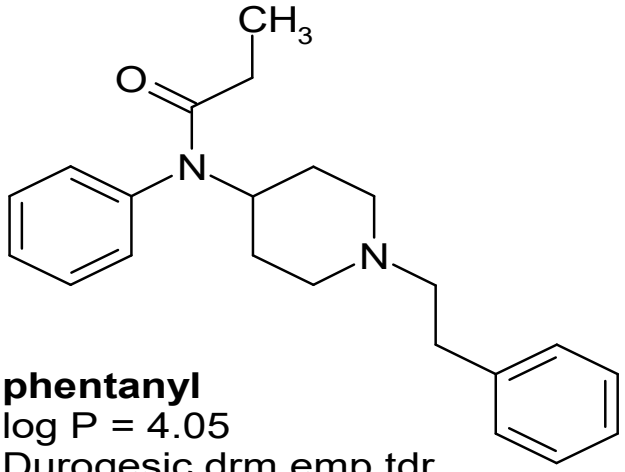
oestradiol
log P = 4.01
Climara drm emp tdr



scopolamine
log P = 0.98



nicotine
log P = 1.17
Nicopatch drm emp tdr
- also buccaly (chewing gums)



phentanyl
log P = 4.05
Durogesic drm emp tdr
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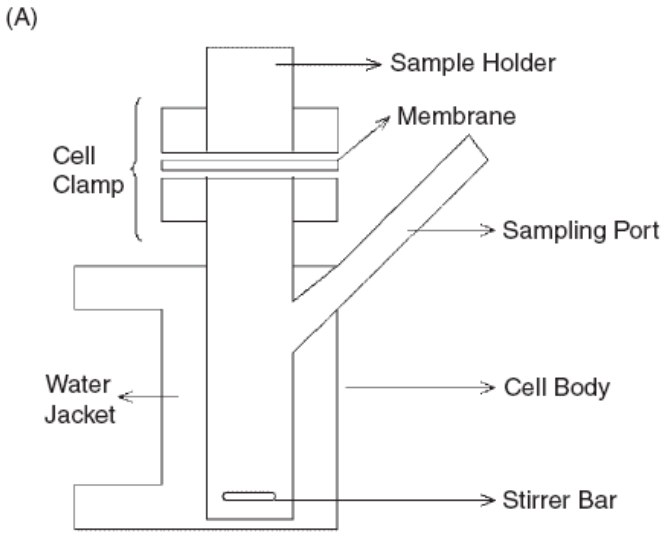
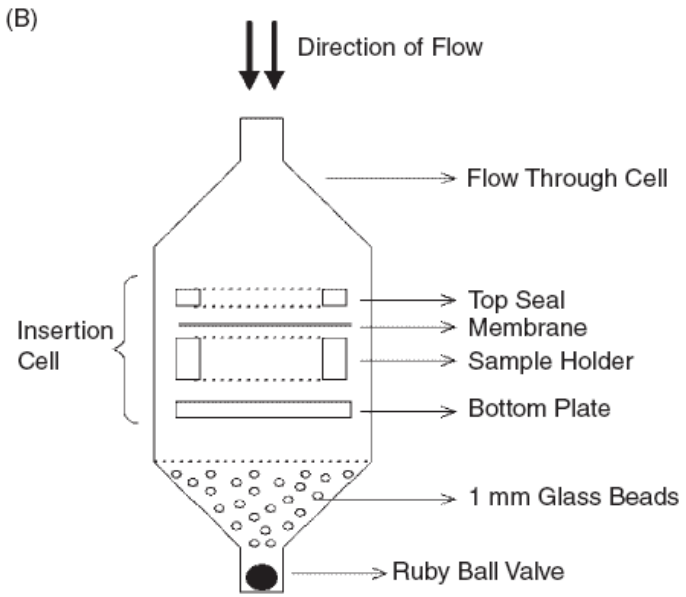
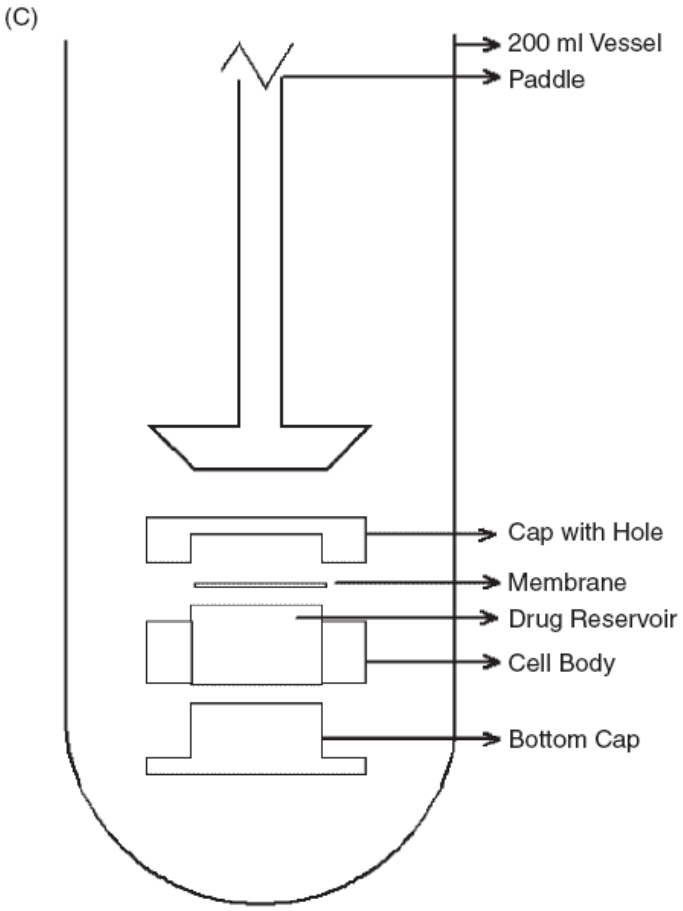
Effentora orm tbl buc

Diffusion apparatuses (cells) used for determination of permeation of a drug through a barrier and thus efficiency of enhancers







A Franz cell
B flow-trough cell
C „Enhancer“ cell

Quantification of efficiency of enhancers

Acceleration ratio AR (=enhancement factor EF)

$$AR = \frac{m_a}{m},$$

where

- m_a is amount of a compound permeated from the vehicle to the target medium without the enhancer
- m is amount of a compound permeated under the same conditions without the enhancer

Flux

= amount of a compound (= a **permeant**) permeated through an **area unit** of the barrier (membrane) with the enhancer and without, and their ratio.

- unit: eg. $\mu g.cm^{-2}.min^{-0.5}$

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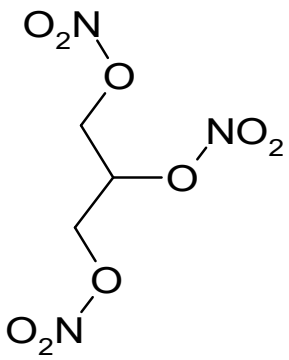

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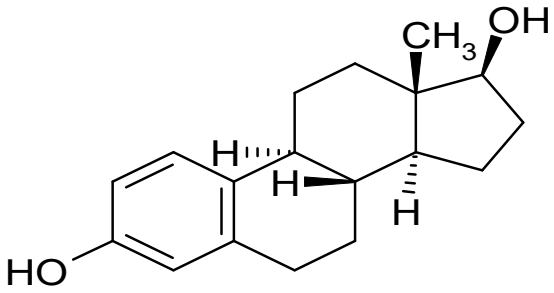

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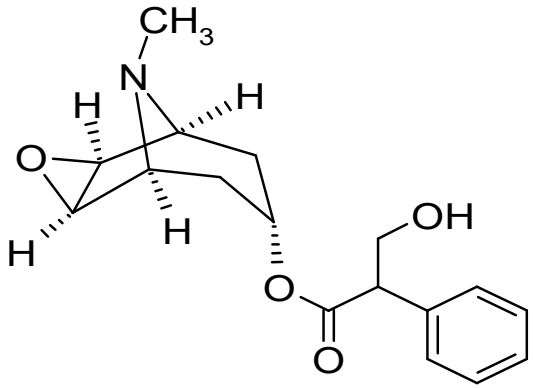

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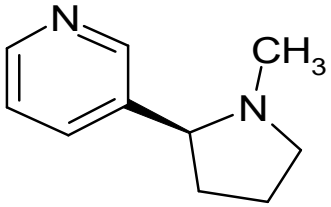

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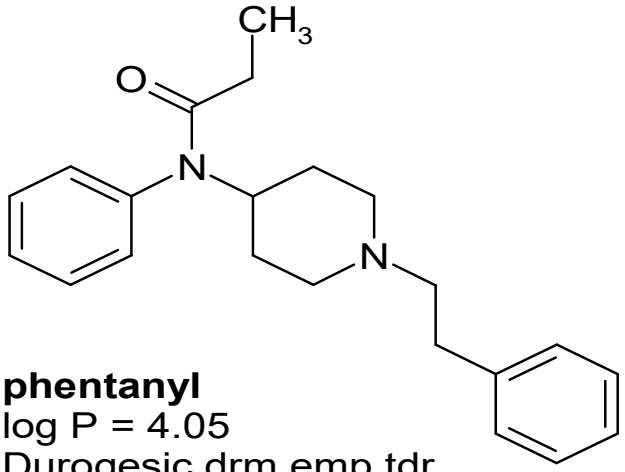

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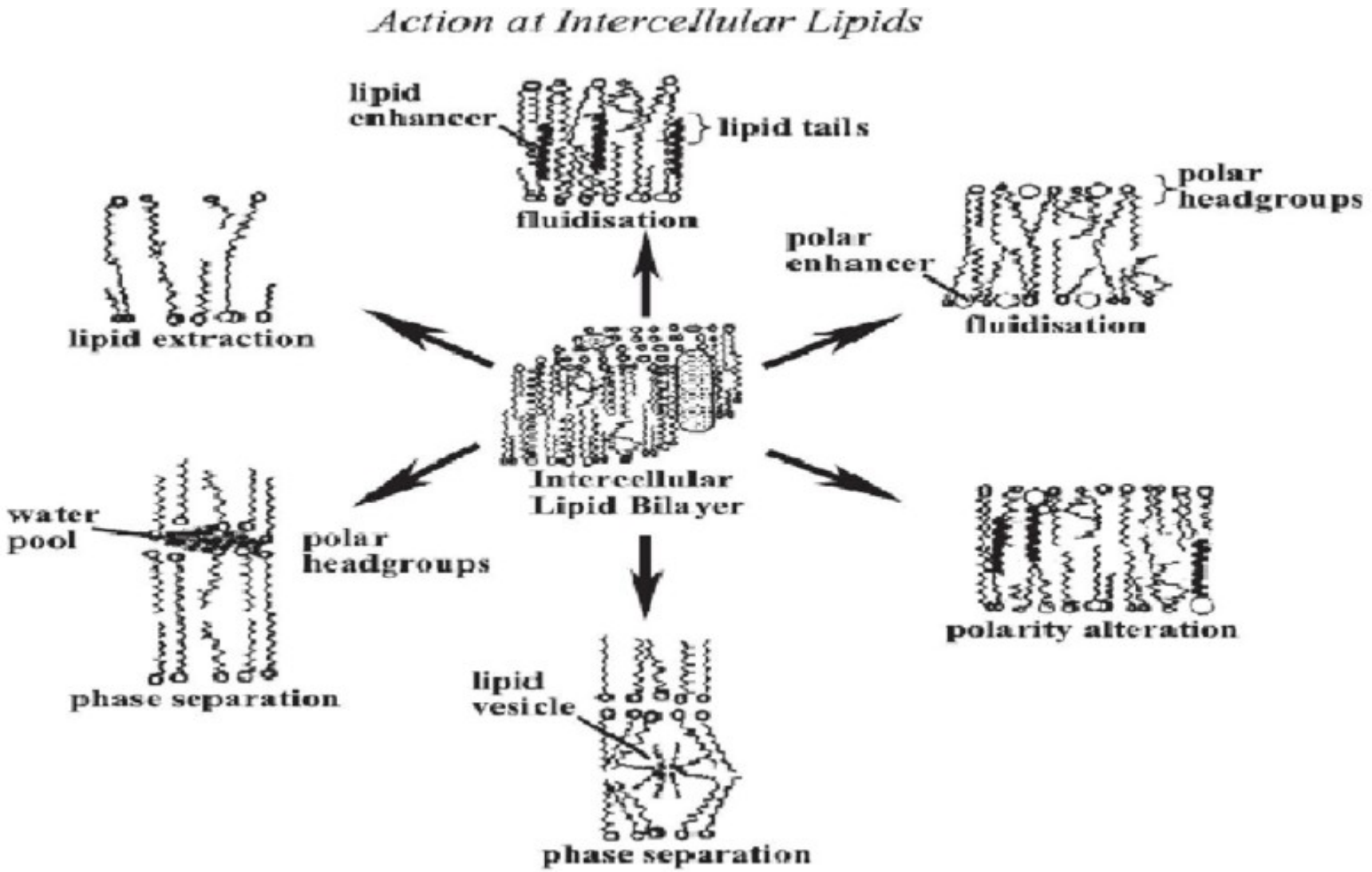
Requirements of ideal transdermal permeation enhancers (Barry 1983) :

1. These materials should be non toxic, non irritating, pharmacologically inert, non allergenic.
2. There should not be any kind of interaction of penetration enhancer with drug and excipient.
3. It should have no pharmacological activity within body.
4. It should be well accepted cosmetically.
5. It should be odorless, tasteless, colorless and inexpensive and have good solvent properties.
6. It should be chemically and physically stable.
7. Duration of action should be both predictable and reproducible and work rapidly.
8. It should be tested in research laboratories.

Some possible mechanisms of action of transdermal permeation enhancers



Main structure types of transdermal permeation enhancers

1. Alcohols
2. Sulfoxides and their derivatives
3. Fatty acids
4. Alkanoic acid esters
5. Terpens
6. ω–amino acid derivatives

6.1 Derivatives of pyrrolidin-2-one (γ–lactams)

6.2 Derivatives of piperidin-2-one (δ–lactams)

6.3 Derivatives of azepan-2-one (ε–lactams)

6.4 Salts of substituted carbamic acids derived from ω–amino acids.

6.5 Esters and amides of ω-amino acids with secondary and tertiary amino groups

7. α–amino acid derivatives
8. Acyclic amides

8.1 Aliphatic amides

8.2 Aromatic amides

9. Analogues of ceramides

·1. Alcohols

•ethanol – the effect found in relation to usage as cosolvent in drug forms; enhances permeation of 5-fluorouracil, steroid hormones, and others

•higher primary alcohols (propanol - hexanol, okcanol - decanol, dodecanol, tetracekanol, hexacekanol, oktacekanol, oleyl alcohol, linoleyl alcohol, and linolenyl alcohol)

• secondary alcohol (isopropyl alcohol, butan-2-ol, pentan-2-ol, and dodecan-2-ol)

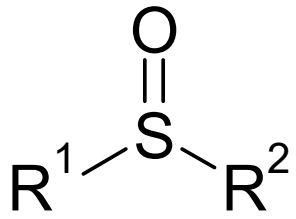
• benzylalcohol

•Probable mechanism of action:

- low-molecular monohydroxylic alcohols increase solubility of a drug in lipid matrix
- more hydrophobic alcanols extract lipids and proteins from *stratum corneum* and thus support diffusion through non-polar way.

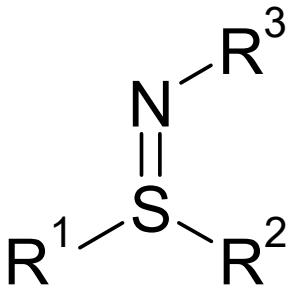
2. Sulfoxides and their derivatives

Sulfoxides

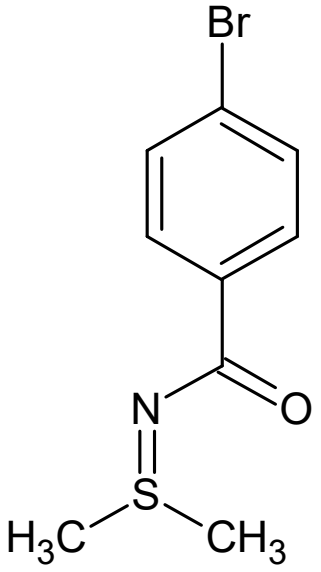


- $R^1 = R^2 = CH_3$ dimethyl sulfoxide – ennhances permeation of many drugs (steroid anti-inflammatory agents, antibiotics, anthelmintics, local anesthetics)
- $R_1 = C_{10}H_{11}$, $R^2 = CH_3$ decylmethyl sulfoxide – polar drugs, eg. zidovudine (AZT)

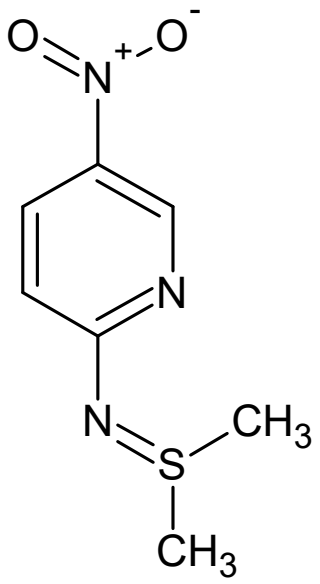
2. Sulfoxides and their derivatives
S,S-dialkylimino sulfuranes



- sulfurous analogues of Schiff bases (azomethins)
- enhance permeation of hydrocortisone through hairless mice skin *in vitro* comparably with Azone®(see further)



S,S-dimethyl-*N*-(4-bromobenzoyl) iminosulfuran



S,S-dimethyl-*N*-(5-nitropyridin-2-yl) iminosulfuran

3. Fatty acids

= saturated or unsaturated aliphatic carboxylic acids with a long chain

- the effect depends not only on the structure of the acid, but also on the structures of the permeant and the vehicle
- the most active saturated:
  - decanoic (capric)
  - dodecanoic (lauric); markedly enhanced testosteron, indomethacin, 5-fluorouracil, and others
- unsaturated: SAR (structure-activity relationships):
  - the number of double bonds (greater number $\Rightarrow$ greater enhancement)
  - their position and configuration on them: the most advantageous in *cis* cinfiguration in the middle of the chain ($\Rightarrow$ disrupting of lipid structure of *stratum corneum* [SC])

4. Alkanoic acid esters

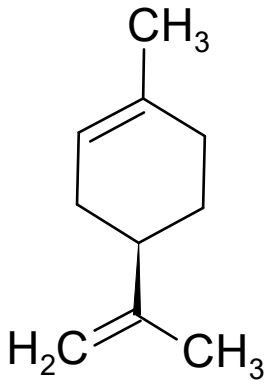
- enhancement effect found in ethyl acetate, butyl acetate, methyl nonanoate, methyl decanoátu, isopropyl myristate and others
- enhance permeation of highly lipophilic compounds (steroids) as well as relatively hydrophilic ones (5-fluorouracil)
- act on lipids of SC, increase the permeability of membranes and values of partition coefficients of both the drug and the solvent into the skin (=between the skin and the vehicle)

5. Terpens

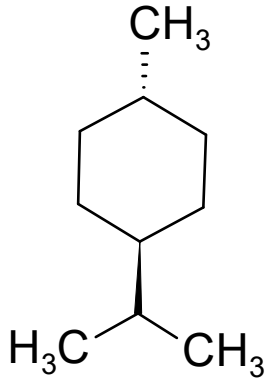
- highly lipophilic, high log P (octanol/water)
- both isolated pure compounds and natural mixtures – essential oils act as enhancers (eg. Peppermint oil – *Menthae piperitae aetheroleum,* Eucalyptus oil – *Eucalypti aetheroleum,* Pine sylvestris oil – *Pini sylvestris aetheroleum* etc.)
- probable mechanism of action: interaction with intercellular lipids of SC

5.1 Cyclic monoterpens

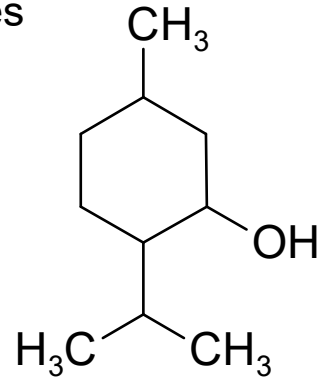
- hydrocarbons, alcohols, phenols, ethers, and ketones were found to be efficient
- ethers, in which O is a part of a ring larger than oxiran were more active than 1,2-epoxides



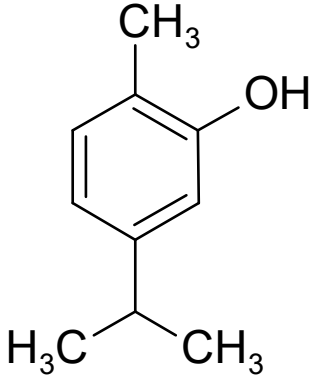
D-limonene



"*trans-p*-menthane"



menthol



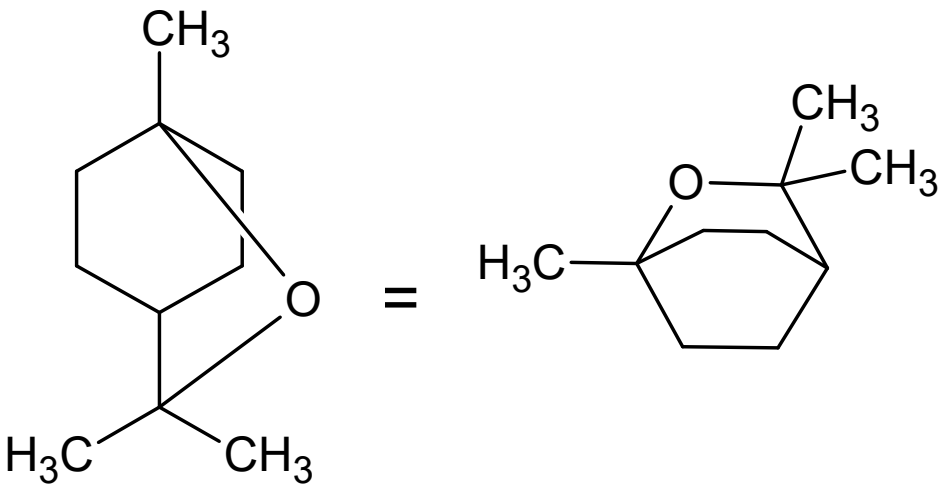
carvacrol

- enhanced permeation of lidocaine, indomethacine and disopyramide trough rat skin *in vivo*

- enhanced permeation of propranolol hydrochloride through hairless mice skin

5.1 Cyclic monoterpens continued

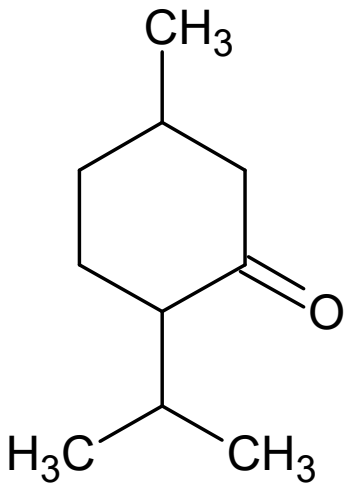
Ethers



1,8-cineole

- enhancement of estradiol permeation
- boat conformation forced by ether bridge probably causes disruption of lamelar structure of lipids

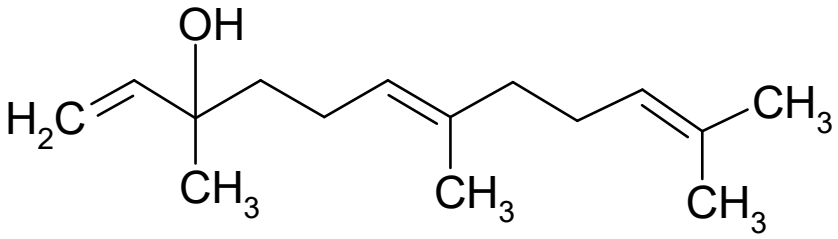
Ketons



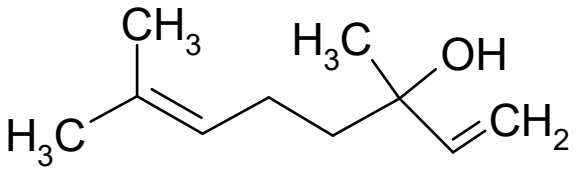
menthone

- permeation of 5-fluorouracil increased 38x

5.2 Linear sesqui- and monoterpens



nerolidol
• flux of 5-fluorouracil through epidermal membrane increased 20x

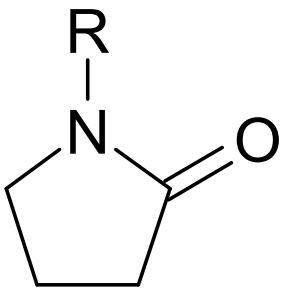


linalol
•enhancement effect on permeation of propranolol hydrochloride through mouse skin depends visibly on concentration

6. Derivatives of ω–amino acids

6.1 Derivatives of pyrrolidin-2-one (γ–lactams)

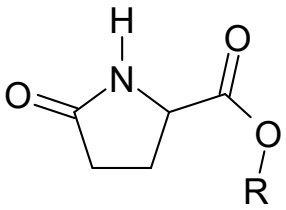
6.1.1 Pyrrolidin-2-one and its *N*-alkylderivatives



R = -H,-C_nH_{2n+1} : enhance permeation of griseofulvin, theophyllin, and oxytetracyclin

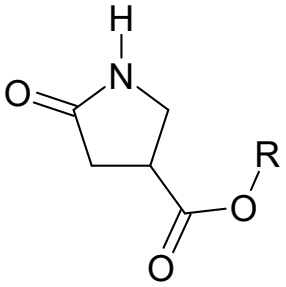
R = -CH_3 ibuprofen, flurbiprofen , mannitol, hydrocortison and progesteron, and also peptides, such as insulin

R = -CH_2COOR^1 hydrocortison 21-acetate; the best R^1 = -$C_{12}H_{25}$ (ER = 67.3)



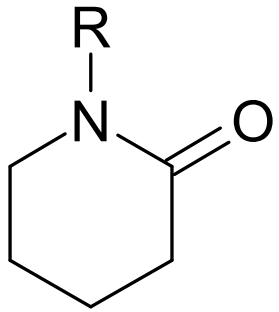
Esters of 2-oxopyrrolidin-5-carboxylic acid

R = -$C_{10}H_{21}$, -$C_{12}H_{25}$, oleyl: enhance enalapril, clonidin



Esters of 2-oxopyrrolidin-4-carboxylic acid

6.2 Derivatives of piperidin-2-one (δ-lactams)

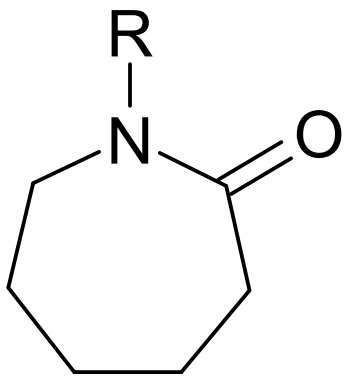


R = $-C_nH_{2n+1}$, the best $-C_{12}H_{25}$ enhanced permeation of 5-fluorouracilu, caffeine, salicyluric acid, salicylic acid, triamcinolone acetonide, and ibuprofen through hairless mice skin.

R = $-CH_2COOR^1$ enhanced permeation of hydrocortison-21-acetate through hairless mice skin; $R^1 = -C_{10}H_{21}$ was the best; better activity than Azon®

R = terpenic rest C_{10}, C_{15}, C_{20} – significantly enhanced permeation of 6-mercaptopurin through excised guinea pig skin

6.3 Derivatives of azepan-2-one (ε-lactams)



R= $-C_nH_{2n+1}$, the most efficient & most studied R= $-C_{12}H_{25}$

Laurocapram, Azon

•enhance significantly both hydrophilic and lipophilic drugs such as morphine hydrochloride, methadon, β–sympatolytics, calcium channel antagonistr, clonazepam, glucokcrtikoids, NSAIDs, some antibiotics and antiviral agents, peptides (insulin and vasopressin), and glycosides (eg. two ester prodrugs of 9-β–arabinofuranosyladenin).

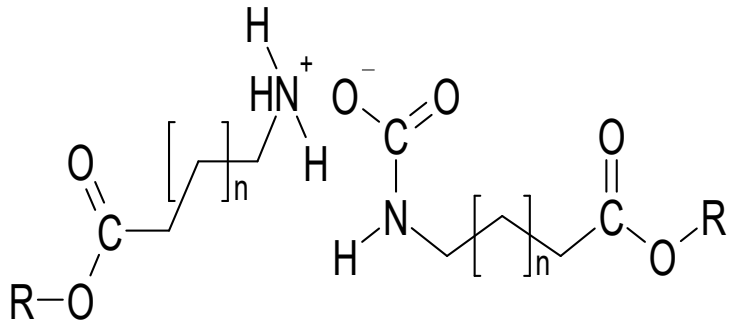
•twelve-carbon chain of Azone corresponds by its size to the skeleton of cholesterol

•Probable mechanism of activity:

•building-in of its molecule into the lamelar membrane of SC results into decrease of interactions between cholesterol and ceramides, and also between cholesterol molecules one with each other.

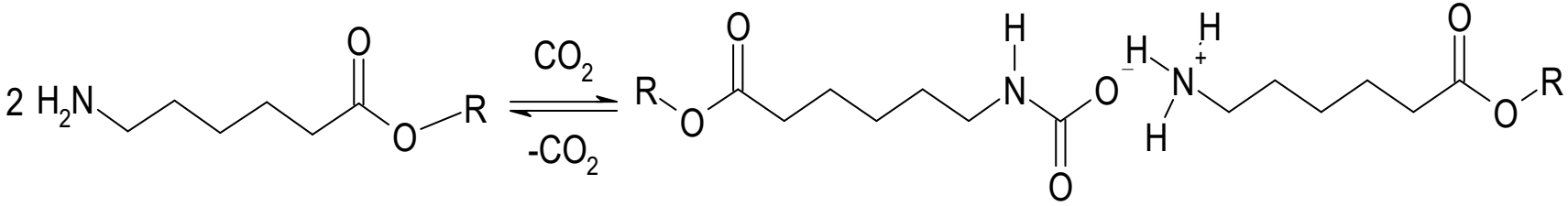
•direct interaction with intercellular lipids increases fluidity of hydrophobic regions of intercellular lamelar structures, which results into decrease of diffusion resistance of the skin

6.4 Salts of substited carbamic acids derived from ω–amino acids



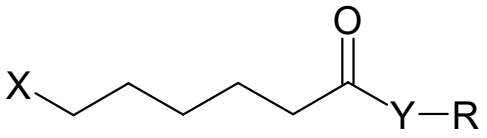
•alkoxycarbonylalkylammonium alkoxycarbonylalkylcarbamates

- the most active R = $-C_{12}H_{25}$, n = 4 Transcarbam 12
- *in vitro* on skin of human donors very active enhancers for theophyllin and 5-fluorouracil, enhance also permeation of other drugs such as aciclovir, some NSAIDs, griseofulvin, etc.

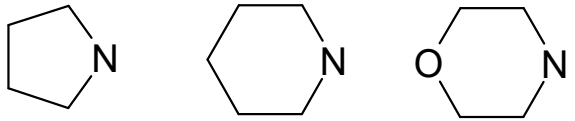


Formation of 5-(alkoxycarbonyl)pentylammonium 5-(alkoxycarbonyl)pentylcarbamate

6.5 Esters and amides of ω-amino acids with secondary and tertiary amino group



X= CH_3NH, C_2H_5NH, $(CH_3)_2N$, $(C_2H_5)_2N$

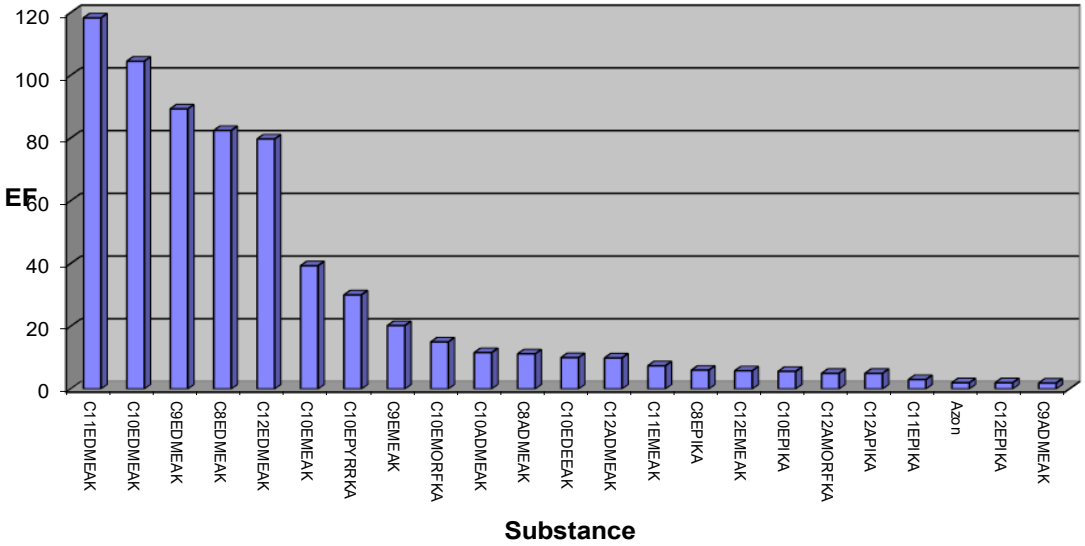


Y= O, NH

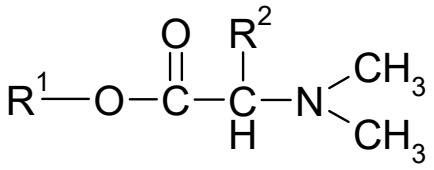
R=cyclohexyl, octyl – dodecyl, octan-2-yl

•significantly enhance permeation of theophyllin from both polar and non-polar vehicle through the human skin *in vitro*

Enhancing factors of tested substances from the hydrophilic vehicle for theophyline as the model permeant



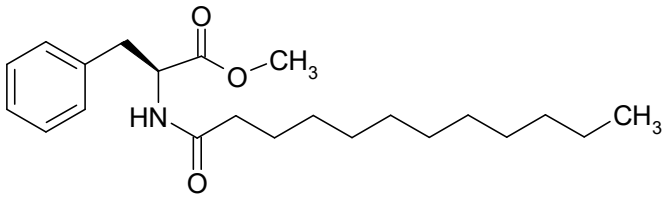
7. Derivatives of α–amino acids



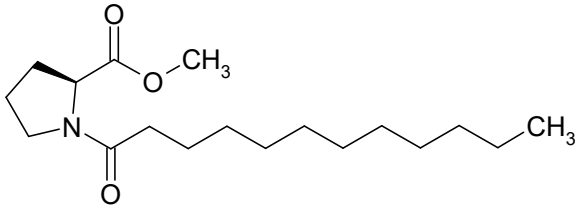
$R^1 = C_{10}H_{21}$, $C_{12}H_{25}$, $R^2 = H$

significant enhancement of permeation of indomethacin through a stripped snake skin *(Elaphe obsoleta)*

$R^1 = C_{12}H_{25}$, $R^2 = CH_3$ enhances permeation of indomethacin, clonidine, and hydrocortisone through the skin of the same snake significatly more than Azone®



•enhance permeation of hydrocortisone through excised hairless mice skin *in vitro*
•ER = 16.5

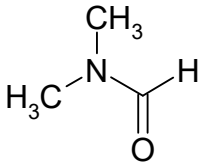


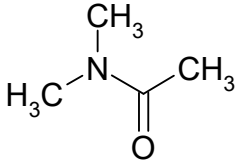
•ER = 13.7

8. Acyclic amides

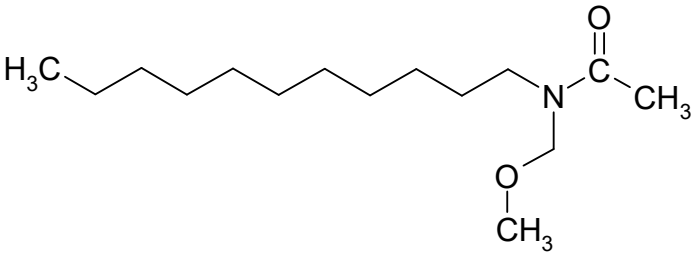
i.e. those, in which amide bond is not a part of a ring

8.1 Aliphatic amides

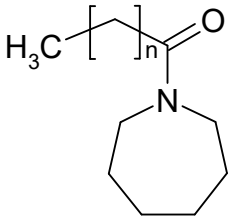




•their effect first reported in 1960s; they support absorption by a polar way by increasing of diffusivity and partitioning, and suppress absorption by non-polar way by lowering of both parameters



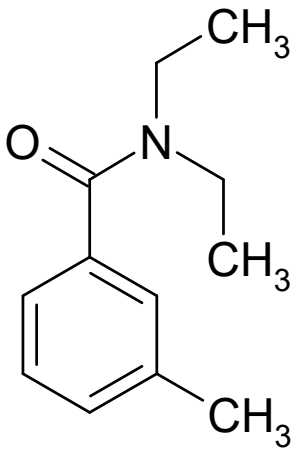
•enhanced permetion of 5-fluorouracil, salicyluric acid, salicylic acid, caffeine, and triamcinolone acetonide through hairless mice skin. The acceleration efficiency increases linearly with decreasing permeant hydrophobicity.



n = 8 hexamethylene octanamide
n = 10 hexamerhylene lauramide

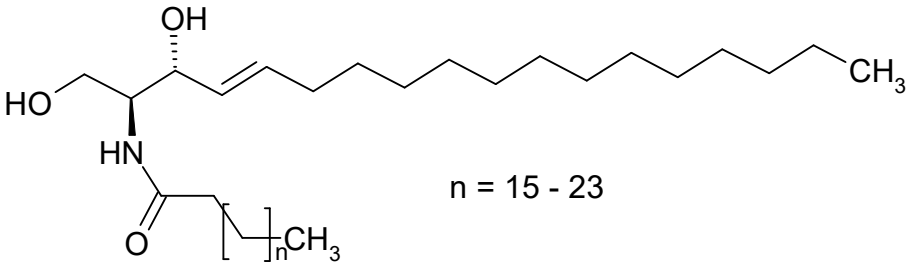
•Azone® analogues; both increased permeation of acetazolamide, cimetidine, guanethidine, sulfacetamide, bunolol, and prednisolone through eye cornea; hexamethylene lauramide, in addition, accelerated the permeation of hydrocortisone through the skin of hairless mice *in vitro* and *in vivo*.

8.2 Aromatic amides

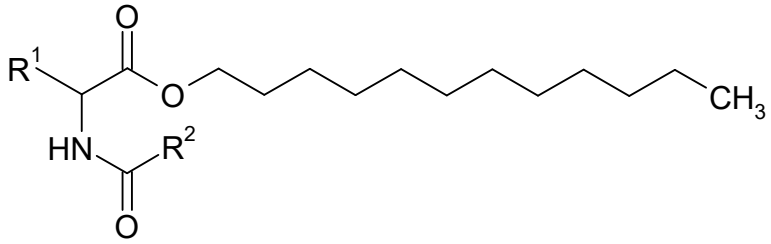


- used as an repellent for repelling of insects or ticks
- at this usage dtermined its low toxicity at dermal aplication in humans
- enhanced permeation of hydrocortisone through hairless mice skin and human skin in *in vitro* v difussion cells.

9. Analogues of ceramides



ceramid 2



series of analogues

R^1 = -H or -CH_2OH, R^2 = alkyl, alkenyl

- tested for enhancement of theophilline permeation from aqueous media through human excised skin
- the most active: R^1 = -H, R^2 = $C_{11}H_{23}$ AP = 12.5

Buccal permeation enhancers

Buccal delivery can:

•suppress the „first-pass“ effect

•avoid the decomposition of unstable drugs with stomach HCl of hydrolases of GIT

•fast absorption thanks to massive vascularistation of buccal mucosa

•absorption is not influenced by changes in velocity of stomach emptying of by food

Factors with an influence to absorption of drugs from the oral cavity:

•pH in weak acids and bases – absorbed in non-dissociated form

•log P

$\Rightarrow$ log D

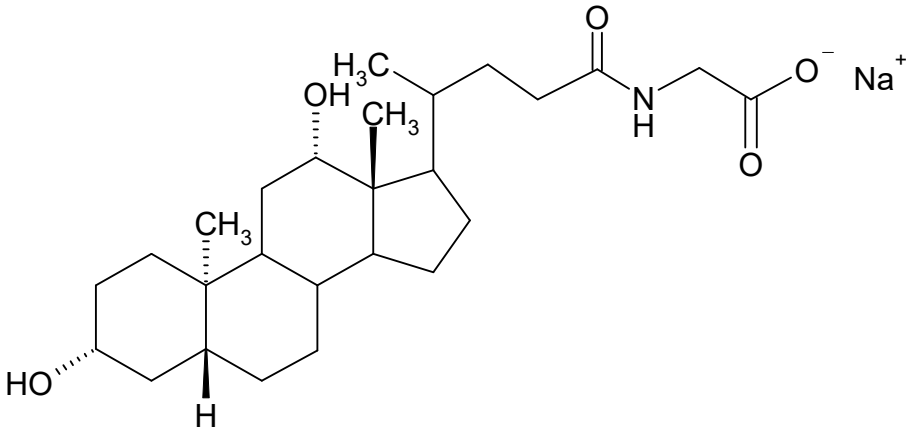
Main ways of permeation through oral mucosa

•transcellular

•paracelullar

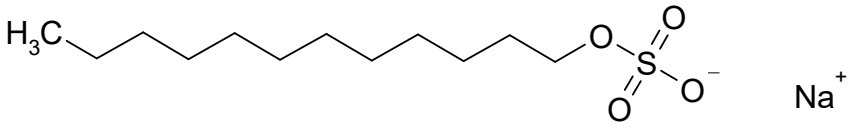
Surfactants and bile acid salts

•act based on surfactant activity to intracellular lipids of mucosa



•sodium glycodeoxycholate - enhanced permeation of morfinium-hydrogensulfate and 2´-,3´-dideoxycytidin through swine mucosa

•causes a decrese of formation of H-bonds between a permeant and lipids of the mucosa (demonstrated by FT-IR)



•sodium dodecylsulfate (sodium laurylsulfate) – enhances permeation of caffeine through swine mucosa in concentrations greater than its critical micellar concentration