Biopharmaceutical aspects of compounding

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european association of hospital pharmacists

Disclosure

- *The content of this presentation is free from any information on healthcare products or services to which the presenter or his relatives have any financial interest or relationship*

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Compounding: what is the relation biopharmacy?

- The therapeutic efficacy of any drug substance is related to:
  - The intrinsic pharmacological and physical properties.
  - The extend and rate of delivery of action, which is determined by:
    1. The release from the dosage form
    2. The release from the dosage form
    3. The rate of the transport from the site of drug release to the site of action

All affected or determined by the formulation and the compounding process

Points 1, 2 and 3 are all determined by:

- The physico-chemical properties of the drug substance
- The physico-chemical properties of the drug product
- The structure of the drug product and location of the drug substance in that structure
- The chosen route of administration

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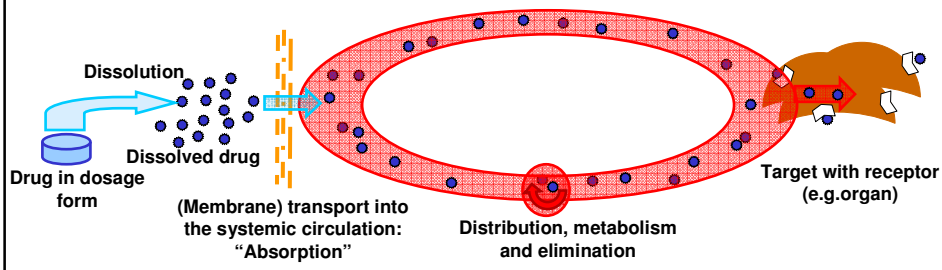
The simplified approach for systemically acting drugs



- Exceptions:
  - i.v. injected drugs
  - locally applied and locally acting drugs
  - targeted drugs

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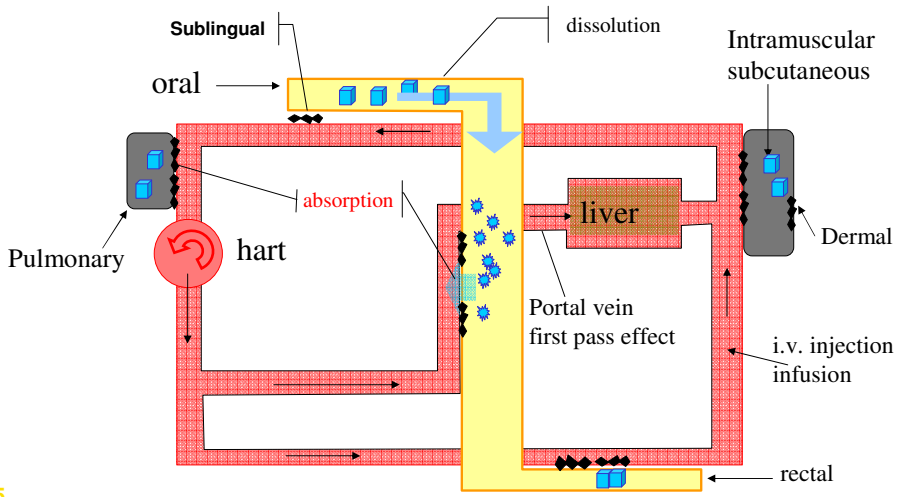
What is the model that we work with for most routes of systemic administration



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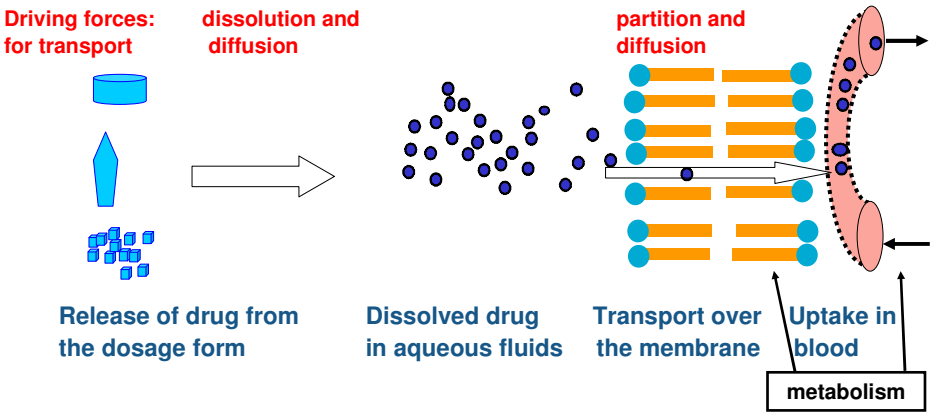
Pharmaceutical availability and bioavailability



Pharmaceutical availability

Bioavailability (e.g. incl. metabolism in intestinal membrane and liver first pass)

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Physico-chemical drug properties relevant to biopharmaceutical aspects and compounding

- Solubility
- Dissolution rate (in what?)
- Molecular structure:
  - acid, base, salt
- Particle size
- Crystalline habit, polymorphism, amorphous, hydrates, etc.
- Partition coefficient (Log P)
- Stability

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Biopharmaceutical aspects of a drug substance related to formulation

- Basics:
  - Pharmacokinetics: distribution, metabolism and elimination.
  - Site of action
  - Intended route of administration
- Related to the route of administration:
  - Physiological conditions at the site of drug release
  - Absorption behaviour of the drug at the site of release

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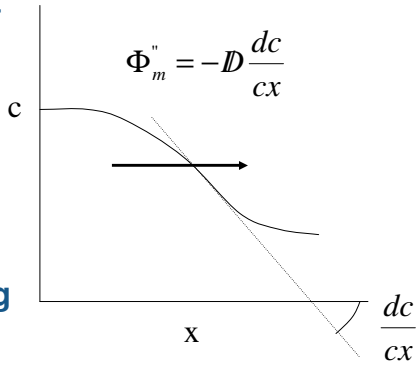
Physico-chemical properties: solubility

- Why is it important?
  - The dissolved drug forms the driving force for the diffusion driven transport
  - Fick's law

$$\Phi''_m \approx -\mathbb{D}\frac{\Delta c}{\Delta x}$$

$$\Phi''_m = -\mathbb{D}\frac{dc}{cx}$$



  - Solubility is a determining parameter for dissolution
  - Dissolved amounts are limited by volume

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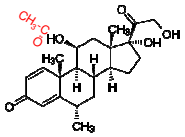
Physico-chemical properties: solubility

- What is a solution?
- What is solubility? (C_s) an equilibrium!
- Solubility in what is relevant?



Solubility

1

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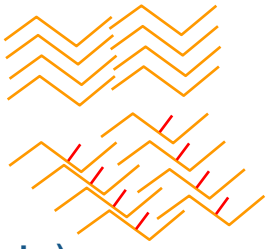

- Factors determining solubility
  - Salt form
  - Crystalline habit
  - Solvent (pH, surfactants, etc.)
  - Particle size (Kelvins's law)

$$C_{s,\,curved} = C_{s,\,flat} * \exp\left(\frac{2\,\gamma_{d,s}\,M_d}{R\,T\,\rho_d\,r}\right)$$

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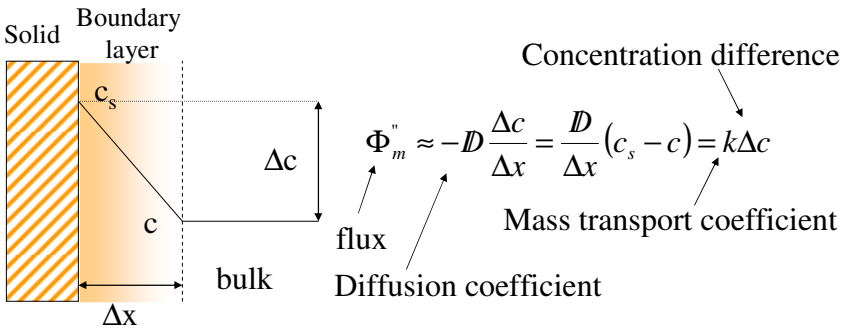
Physico chemical properties: Dissolution rate



The Noyes-Whitney equation:

$$\Phi_m \approx -\mathbb{D}.\frac{\Delta c}{\Delta x}.A = \frac{\mathbb{D}}{\Delta x}.A.(c_s - c) = k.A.\Delta c$$

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Physico chemical properties: Dissolution rate

- **The Noyes-Whitney equation:**

$$\Phi_m \approx -\mathbb{D}.\frac{\Delta c}{\Delta x}.A = \frac{\mathbb{D}}{\Delta x}.A.(c_s - c) = k.A.\Delta c$$

- **How to increase the dissolution rate:**
  - **Surface: particle size and disintegration**
    - 1 cube: 1 cm 6 cm^2
      10^6 cubes: 100 µm 600 cm^2
      10^{12} cubes 1 µm 60.000 cm^2
    - $S_m = 6/(d.\rho)$
      - For cubes or spheres: d = diameter ρ = density
  - **Salt form**
  - **Crystalline habit or amorphous material**
  - **Consider the solvent: (pH, surface active)**

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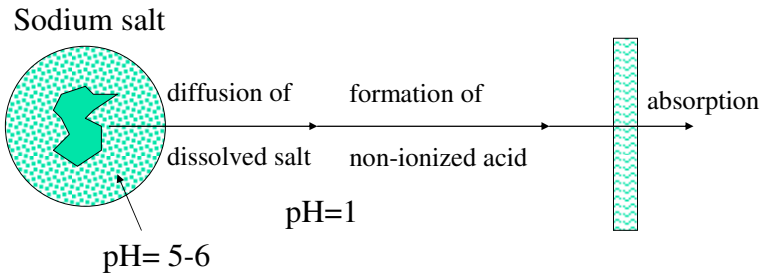
Physico chemical properties: Dissolution rate

- **Salt form:**

$$\Delta c \approx c_s \Rightarrow \Phi_m = k.c_s.A \quad c_s = [HA] + [A^-] = c_o\left(1 + \frac{K_Z}{[H_3O^+]}\right)$$

- **Sodium salt of an acid in the stomach**



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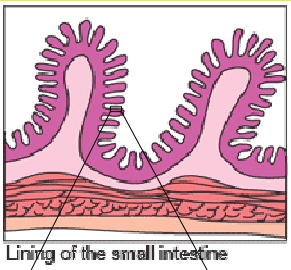
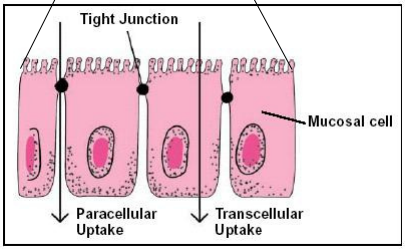
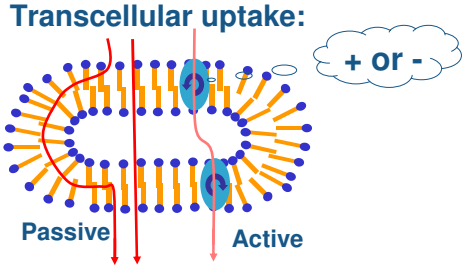
Mechanisms of membrane transport





- **Transcellular uptake:**



- **Paracellular uptake:**
  - **Tight junctions, aqueous pores, intercellular spaces:**
  - **Where?**
    - **Intestinal tract**
    - **Oral cavity**
    - **Nasal cavity**
    - **Conjunctiva**
    - **lungs**

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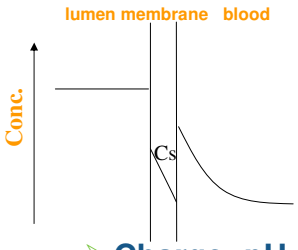
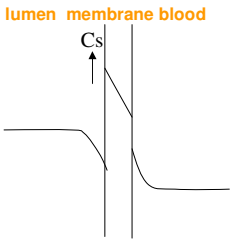
Absorption of a drug:
solubility, dissolution, charge, pH and metabolism

- What determines the route of membrane passage and the efficacy of absorption?
  - Log P (what is a partition coefficient?)

Hydrophilic drug



Lipophylic drug



- What would be the effect of an increase in aqueous solubility:
  - For a hydrophylic drug
  - For a lipophylic drug

  - Charge: pH
    - also for transcellular uptake
  - Transporters
  - First pass metabolism

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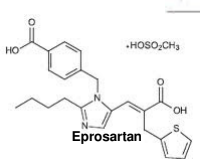
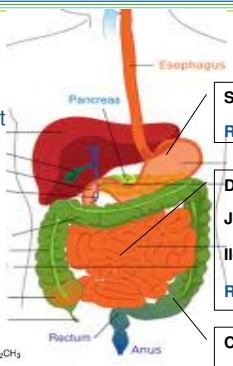
Absorption and pH

- pH-partition hypothesis:
  - due to the higher lipophylicity of non charge molecules the non-ionized fraction of acids and bases forms the driving force for transport of lipophylic membranes.
- Henderson-Hasselbalch equation:
- Acid: fraction non-ionized = $[1 + 10^{pH-pKa}]^{-1}$
- Base: fraction non-ionized = $[1 + 10^{pKa-pH}]^{-1}$

- Example: acetylsalicylic acid, pKa = 3.0
- Stomach: pH = 2.0
  - Non-ionized = 90.9 %
- Small intestine pH = 6.8
  - Non-ionized = 0.02%



- Take also lipophilicity into acc...
  - Driving force = NIF. $10^{(log\ P)}$ = NIF . P.C.
    - Log P : of the non-ionized molecule
    - P.C.: partition coefficient
    - NIF: non-ionized fraction



Stomach: pH 1.5 – 5.0
Res.time: 1.5 hr (0.2 - 6)

Duodenum: pH 2.0 - 6.8
Jejunum: pH 6.8
Ileum: pH 6.8 - 7.4
Res.time: 4.5 – 6 hr

Colon: pH 7.4 – 6.0
Res.time: 6 - 16 hr

In general one charged group is not prohibitive for passive absorption more groups are!

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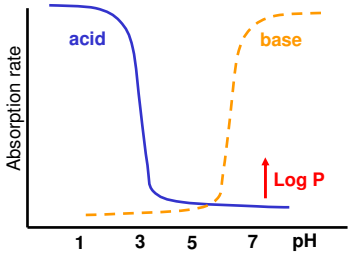
Absorption from the G-I tract: a summary

- **Passive transport:**
  - Solubility / dissolution rate
  - pH
  - Log P
  - Surface
  - Volume
  - First pass metabolism



- **Active transport:**
  - Solubility / dissolution rate
  - Transporters
    - Increase absorption:
      - E.g. amino acid transporters for ACE-inhibitors
    - Efflux transporters: decrease absorption:
      - PGP-pump
      - Inhibitors
  - First pass metabolism
    - E.g. cyp's
    - inhibitors

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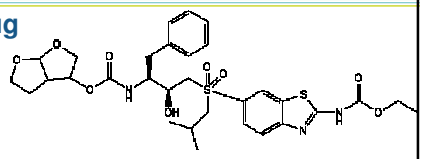
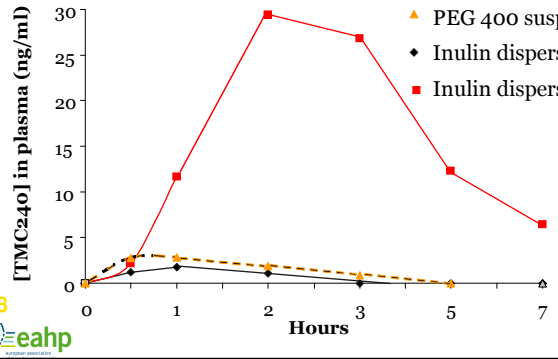
Formulating class IV drugs poor solubility + eflux transporters

- TMC 240: experimental class IV drug
- Ritonavir: glycoprotein-P inhibitor
- Formulations
  - Microsuspension in PEG
  - Nanodispersion in inulin
  - Administration to dogs





PEG 400 suspension (n=0/3)
PEG 400 suspension + ritonavir (mean, n=3/3)
Inulin dispersion tablet - ritanovir (n=1/3)
Inulin dispersion tablet + ritonavir (mean, n=3/3)

A 30-fold increase in bioavailability

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The biopharmaceutical classification system: Help for a complex system

Heaven

BCS class I -high permeability -high solubility	**BCS class II** -high permeability -low solubility
BCS class III -low permeability -high solubility	**BCS class IV** -low permeability -low solubility

Permeability

Solubility

Hell

- **Permeability:**
  - Extend of absorption after administration is >90%
  - In vitro analysis (e.g. caco2 cells transport or ussing chambers, etc.)
- **Solubility:**
  - For oral drugs: a drug has a high solubility when the highest dose dissolves in 250 ml of aqueous buffer with a pH between 2 and 7.5.
  - What about a rectal drug: 250 ml still relevant?

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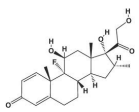
Solubility and dose number

- Dose number (DN) is a dimensionless parameter that links solubility (Cs) to dose (d) and volume available for dissolution (V)
- $DN = \frac{d}{V \cdot Cs}$
- DN < 0.1 no effect of solubility on absorption rate
- DN > 10 solubility will affect absorption rate and bioavailability
- DN 0.1-10 solubility may affect absorption rate and bioavailability
- Example:
  - Dexamethasone: Cs=89 mg/L
  - Normal oral dose: 0.5 -7.5 mg/dose, stomach: 1 l of fluid (= low)
    - $DN = 7.5 \cdot (89 \cdot 1)^{-1} = 0.08$
  - The dose for acute pyodermia gangrenosum is 300 mg.
  - What if we prepare capsules with 300 mg dexamethasone
    - $DN = 300 \cdot (89 \cdot 1)^{-1} = 3.3$ (which is rather close to 10!)
  - A 5 ml enema with a dexamethason 7.5 mg suspension:
    - $DN = 7.5 \cdot (89 \cdot 0.01)^{-1} = 8.4$ (which is rather close to 10!)



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The role of first pass metabolism

- A drug:
  - dose of 50 - 150 mg/dose
  - Half live: 2 - 3 hrs
  - Administration frequency 3 – 4 times a day
  - Bioavailability: 50%
    - Reason for poor bioavailability: first pass enzymatic metabolism in the liver
    - Bioavailability is still 50% because the metabolism is saturated at the higher blood levels
- Can we reduce the dosing frequency by making an oral slow release product with a 100 – 300 mg dose that is to be taken only twice a day?

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Physico-chemical drug properties relevant to biopharmaceutical aspects and compounding

- Solubility
- Dissolution rate (in what?)
- Molecular structure:
  - acid, base, salt
- Particle size
- Crystalline habit, polymorphism, amorphous, hydrates, etc.
- Partition coefficient (Log P)
- Stability

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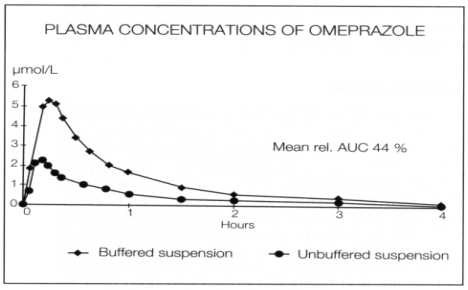
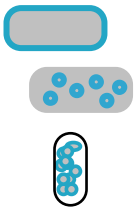
The relevance of stability:

- Can the drug substance resist: process, excipients and physiological environment?
- Can we crush proton pump inhibitors and use them in capsules?

	Omeprazole	Lansoprazole	Pantoprazole
pH=2	105 sec	85 sec	195 sec
pH=7	23 hrs	13 hrs	39 hrs

from:
Pilbrant, 1993





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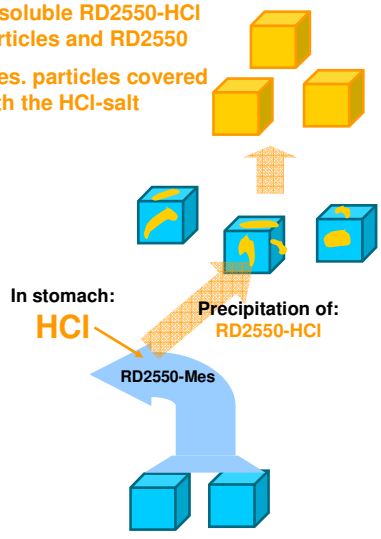
Physiological aspects of salt formation and solubility

- RD2550, an amine, solubility of different salts in water:
  - Free base: 17 µg/ml
  - HCl : 8 µg/ml
  - Sulphate : 140 µg/ml
  - Mesylate : 350 µg/ml
- Capsules containing 300 mg RD2550-mesylate were administered orally to dogs:
  - Bioavailability <13%
  - No permeation problems over caco-2 cells
  - No signs of first pass metabolism
  - Significant amounts of drug in the faeces



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Structure

- Often the structure (arrangement of excipients or different phases) of a product determines its functionality:
  - A proton pump inhibitor should be inside its e.c. layer, and the layer should be intact
  - W/O emulsions behave different from a O/W emulsion on the skin. Related to the lipophilicity of the drug.
  - Dissolution of lipophilic drugs in oily injections (s.c. i.m.) results in depot injections
  - The release rate of a depot injection based on a suspension of a highly insoluble drug depends on the particle size of the drug
  - etc.

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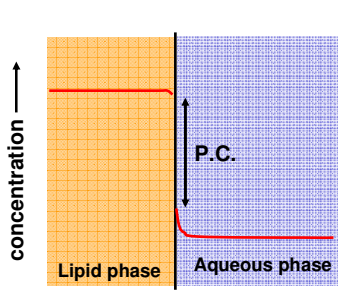
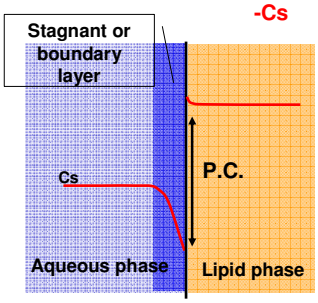
Phase transport and partition coefficient

- The driving force for transport over oil-water interfaces:
  - Partition coefficient
  - Concentration differences in boundary layer
  - Thickness of boundary layer
- Rate determining parameter:
  - Lipophilic substance
  - Lipid to aqueous layer: P.C.

Aqueous to lipid layer: -stagnant layer -Cs





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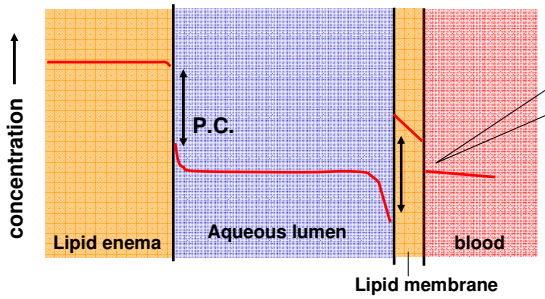
Lipid drug dissolved in an oily enema



Why is a lipophilic drug transported from the lipid membrane into the aqueous blood?

- Lipophilic drug substances are better not formulated in a lipid enema or suppository, but better in n aqueous base (aqueous buffer, or PEG suppository): smaller particles result in a faster dissolution and absorption
- How can we increase the lipid to water transport of lipophilic substances?
- In which type of preparations is this applied?

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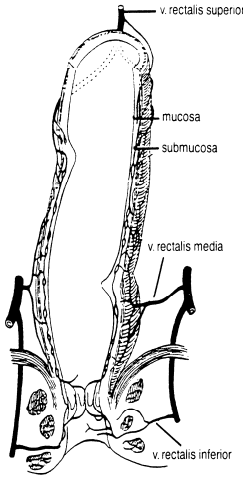
Some aspects of major routes of systemic administration:

- Rectal route:
  - Only 5-15 ml of aqueous liquid for dissolution
  - Immediate start of release and absorption
  - Limited pH variation: 5.5 - 6.5
  - Liver first pass reduction with about 30%
  - Sensitive to irritation, e.g. surfactants
- Question: should the drug particles of a hydrophylic drug in a fatty suppository be large or small when a rapid onset of action is desired?



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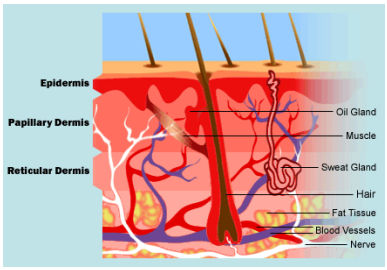
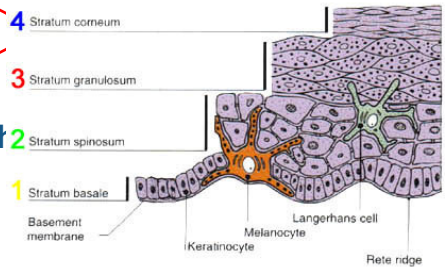
Some aspects of major routes of systemic administration:

- Dermal route:
  - The skin is a highly lipophilic barrier
  - Stratum corneum is the major barrier
  - Transport also via hair follicles and sebum glands
  - Little liquid for dissolution
  - Lipophilic drugs
  - O/W creams
  - Patches of polymers or with rate determining membranes that slowly release the drug





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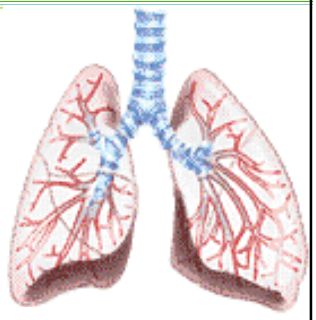
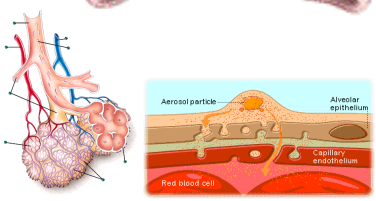
Some aspects of major routes of systemic administration:

- Pulmonary route:
  - Airways:
    - Suitable for "small" hydrophilic and lipophilic molecules
    - Limited metabolic capacity
  - Alveoli:
    - Most leaky membrane (5 nm tight junctions) in our body, limited metabolic capacity
    - Absorption of molecules up to 20 KDa
  - Performance highly determined by aerosol and inhalation parameters:
    - Aerosol particle size
    - Inhalation flow and manoeuvre
  - Protein absorption?





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Some aspects of major routes of systemic administration:

- Intra-oral route:
  - Sublingual: fast
  - Buccal: slower
- Nasal route:
- Fast absorption of small (lipophilic) molecules
- Limited volume for dissolution
- No liver first-pass metabolism

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Compounding: what is the relation biopharmacy?

- The therapeutic efficacy of any drug substance is related to:
  - The intrinsic pharmacological and toxicological properties.
  - The extend and rate of delivery to the site of action, which is determined by:
    1. The release of the drug from the dosage form
    2. The site of drug release from the dosage form
    3. The efficacy of the transport from the site of drug release to the site of action: absorption and first pass metabolism
- The points 1, 2 and 3 are all determined by:
  - The physico-chemical properties of the drug substance
  - The physico-chemical properties of the drug product
  - The structure of the drug product and location of the drug substance in that structure
  - The chosen route of administration

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Physico-chemical aspects relevant to compounding:

- Take the right salt
- Take the right crystal and don't change it
- Consider processes that change the particle size
- Consider the particle size in relation to the solubility and dose of a drug
- Consider the solubility in relation to the dose and the volume available for dissolution
- Consider the (variations in) pH in which the drug has to dissolve
- Consider the nature of the absorption route in relation to the drug properties (variations in: aqueous pores, metabolic activity, surface, etc.)
- Understand the structure of your dosage form in relation to functionality
- Understand the release mechanisms from your dosage form in relation to the physico-chemical properties and structure

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