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Drug delivery approaches, routes of administration, prolonged release preparations.

Ondřej Zendulka

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Drug dosage forms (DDF)

- final form in which is the drug administered to patients
- consists of active drugs and vehicles
- **enables the drug to be administered by the selected route**
- helps to administered accurate dose of the drug

DDF

- protection of active substance (AS) against environmental influences (light, humidity)
- protection of AS in human body (↓ pH in stomach)
- adjustment of organoleptic properties (smell, taste)
- influence of the PK properties:
  - release adjustment
  - targeted distribution of AS

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Pharmacological differences between administration routes

Pharmacodynamic

- change in the character of the drug‘s effect

Pharmacokinetic

- local vs. systemic effect => local vs systemic administration
- the change of the latence of the effect onset/duration. or toxicity

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Administration/effect of drug

Local

- drug absorption is limited
- effect aimed on target tissue/organ
- low risk of AE
- effect depends upon final concentration

Systemic

- drug is absorbed to systemic circulation
- possible influence on whole body
- higher risk of AE
- effect depends on dose, bioavailability and DDF

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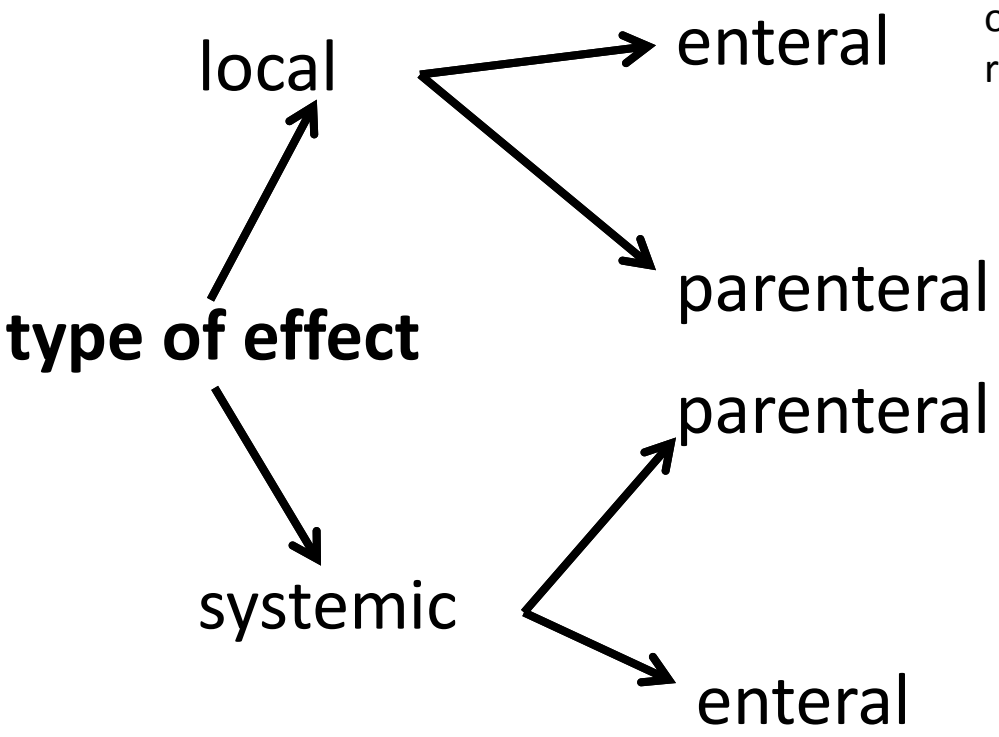
Klasifikace aplikačních způsobů



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Classification of administration routes

- with regerd to the disrupotion of natural protective barriers

Non-invasive

- vaginal, (intrauterine?)
- sublingval
- epicutaneous
- oral
- intranasal
- inhalational
- rectal

Invasive

- intravenous
- intraartrerial
- intraoseal
- intramuscular
- subcutaneous
- intradermal
- implants

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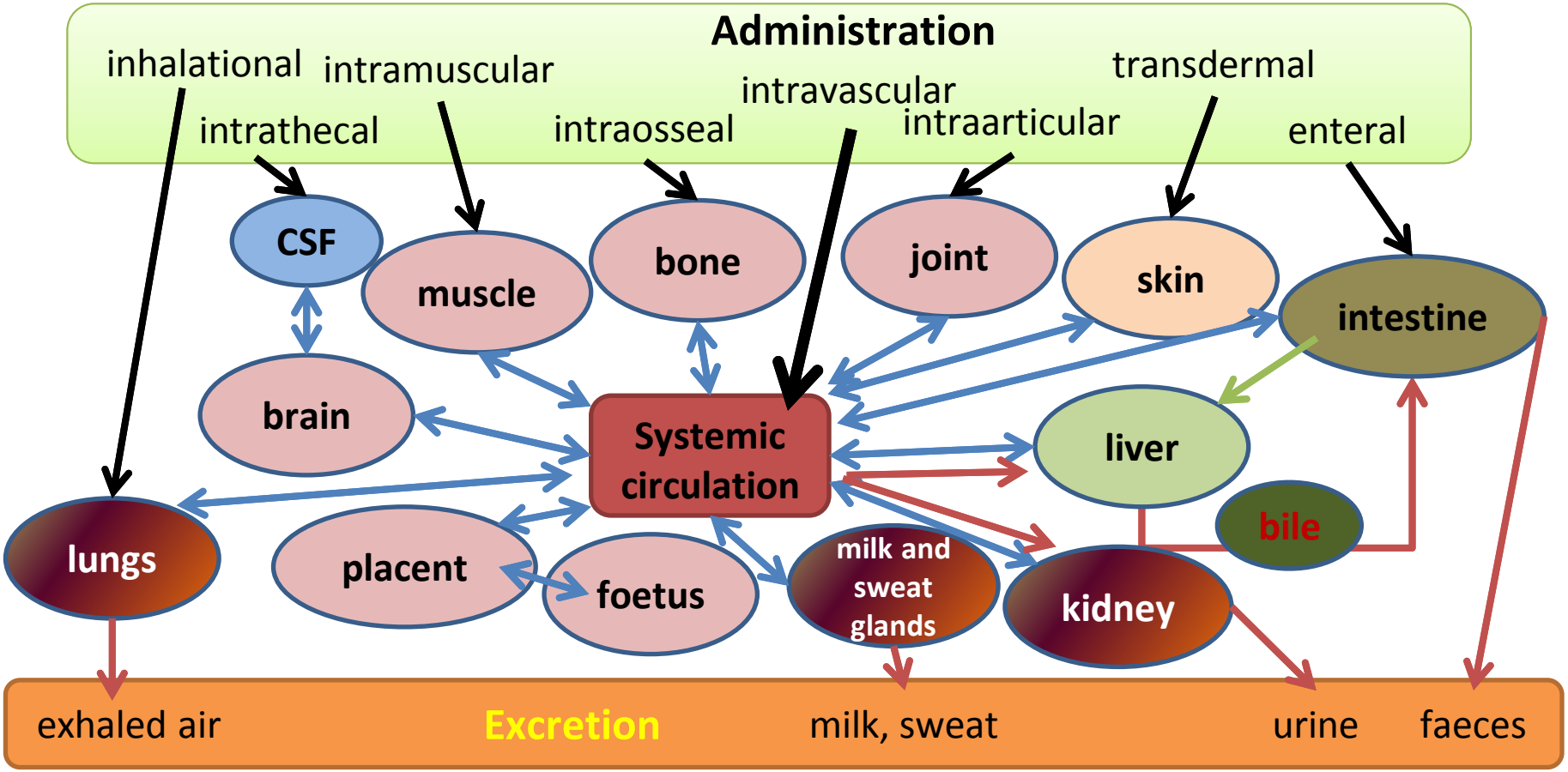
Systemic drug administration



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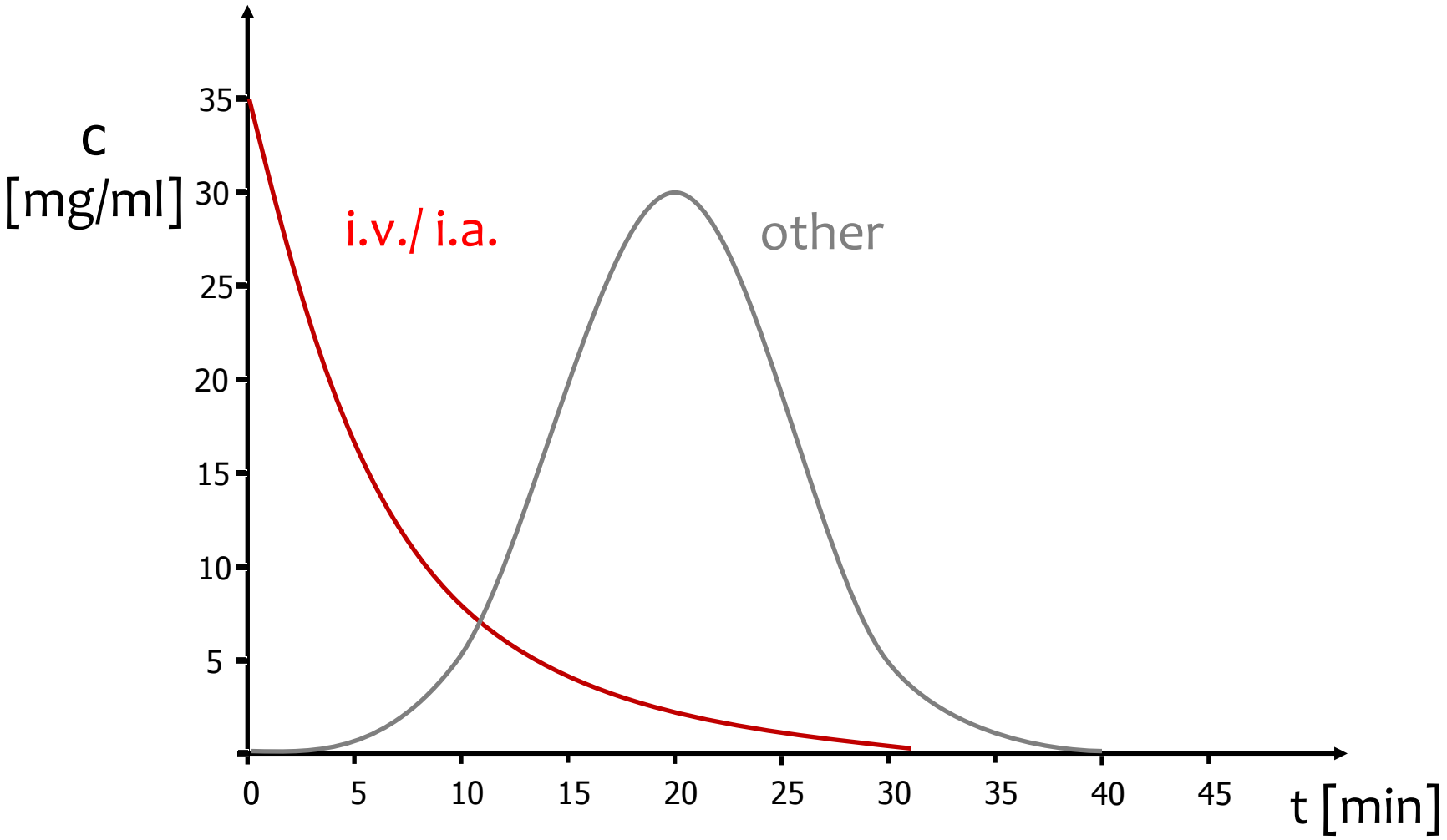
Types of administration with regard to the drug‘s profile of plasma levels

Single (bolus) drug administration

- all DDF and routes of administrations
- drugs are not cumulated in the body or in case of vaccination

Repeated drug administration

- for the chronic therapy
- following dose is administered before the previous is fully eliminated = drug cummulation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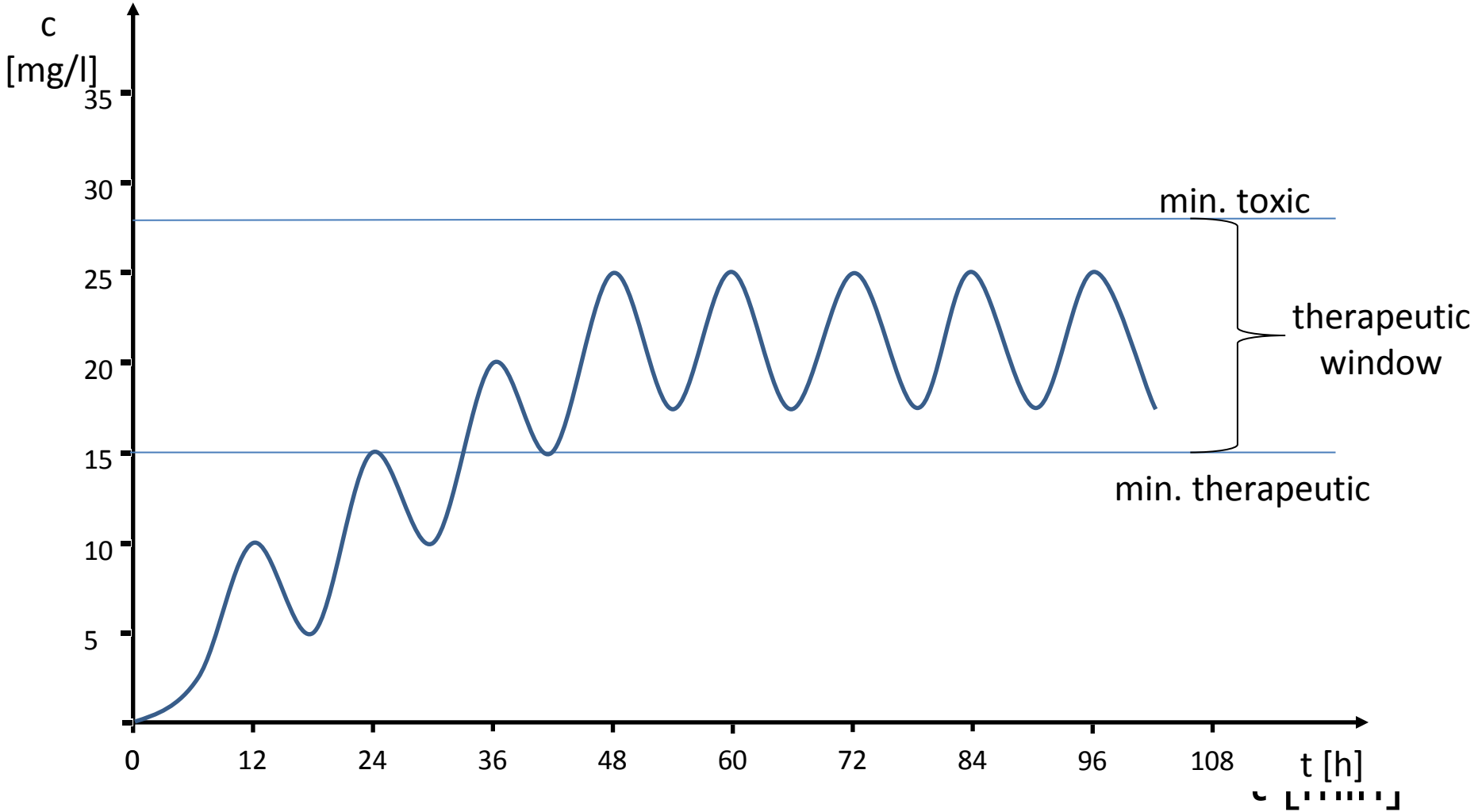
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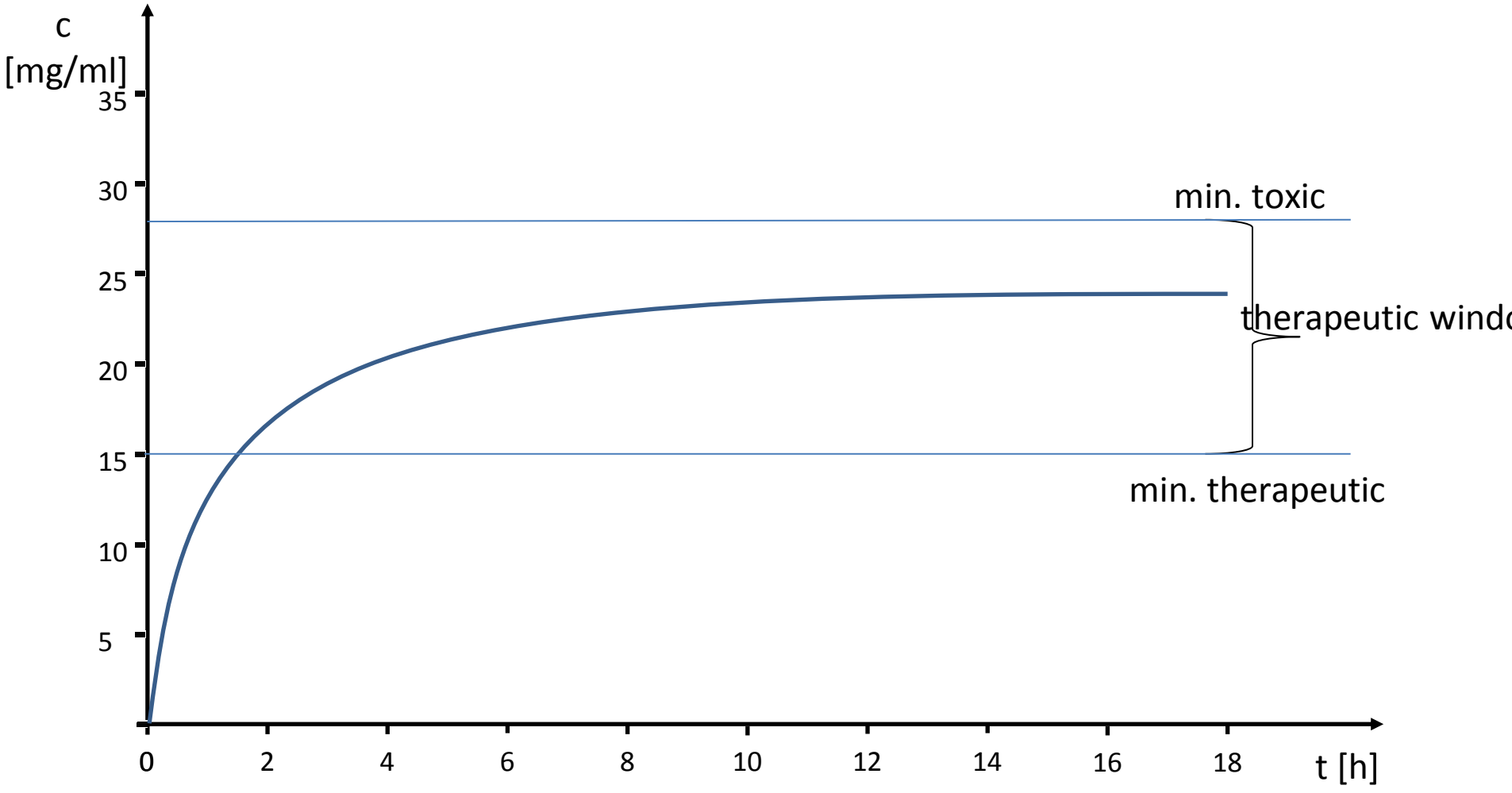
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Administration routes for local effect

- intraurethral, intravesical, intracavernal
- dental, gingival, oral
- endotracheopulmonal
- intraaural
- intraamniotic
- intracoronar
- conjunctival, intrathecal, intraocular, intraarticular

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Conjunctival administration

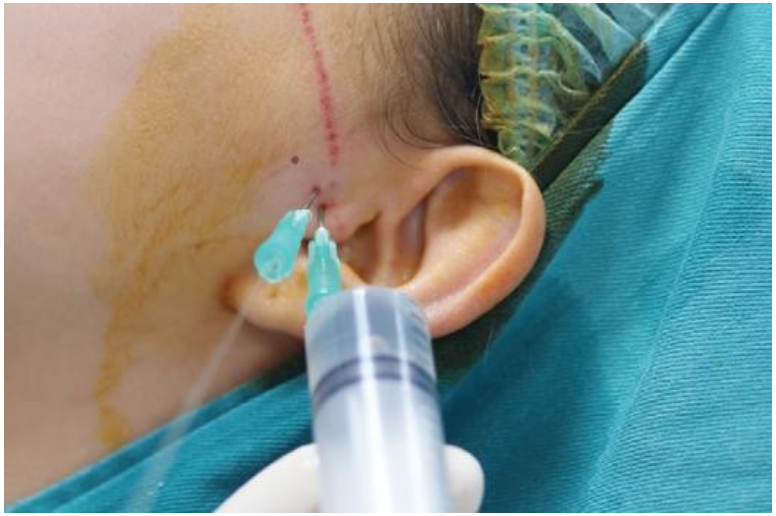
- usually eye drops and ointments
- local effect
- risk of systemic AE
- specific quality requirements - sterility

Intrathecal/intracerebral/intracerebroventricular administration

- to the subarachnoideal space/ brain/ brain vetricles

Intraarticular administration

- analgesics/antiphlogistics
- hyaluronic acid
- for local effect



Intraocular administration

- intravitreal implants in macular degeneration

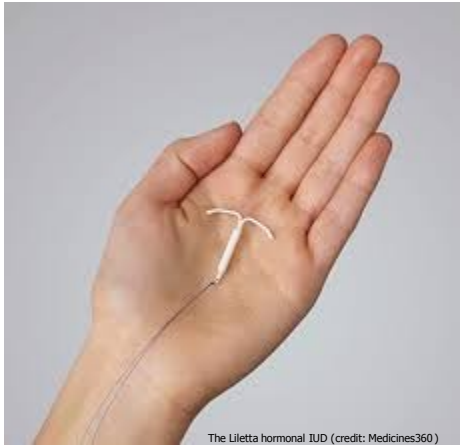
Vaginal, endocervical, intrauterinal

1. local effect

- minimum of AE
- specific adjuvants ↓ pH
- antibiotics, antimycotics, antiparasitics

2. systemic effect

- vaginal rings intrauterine devices
- controlled drug release
- contraceptives



The Liletta hormonal IUD (credit: Medicines360)

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Epicutaneous/transdermal administration

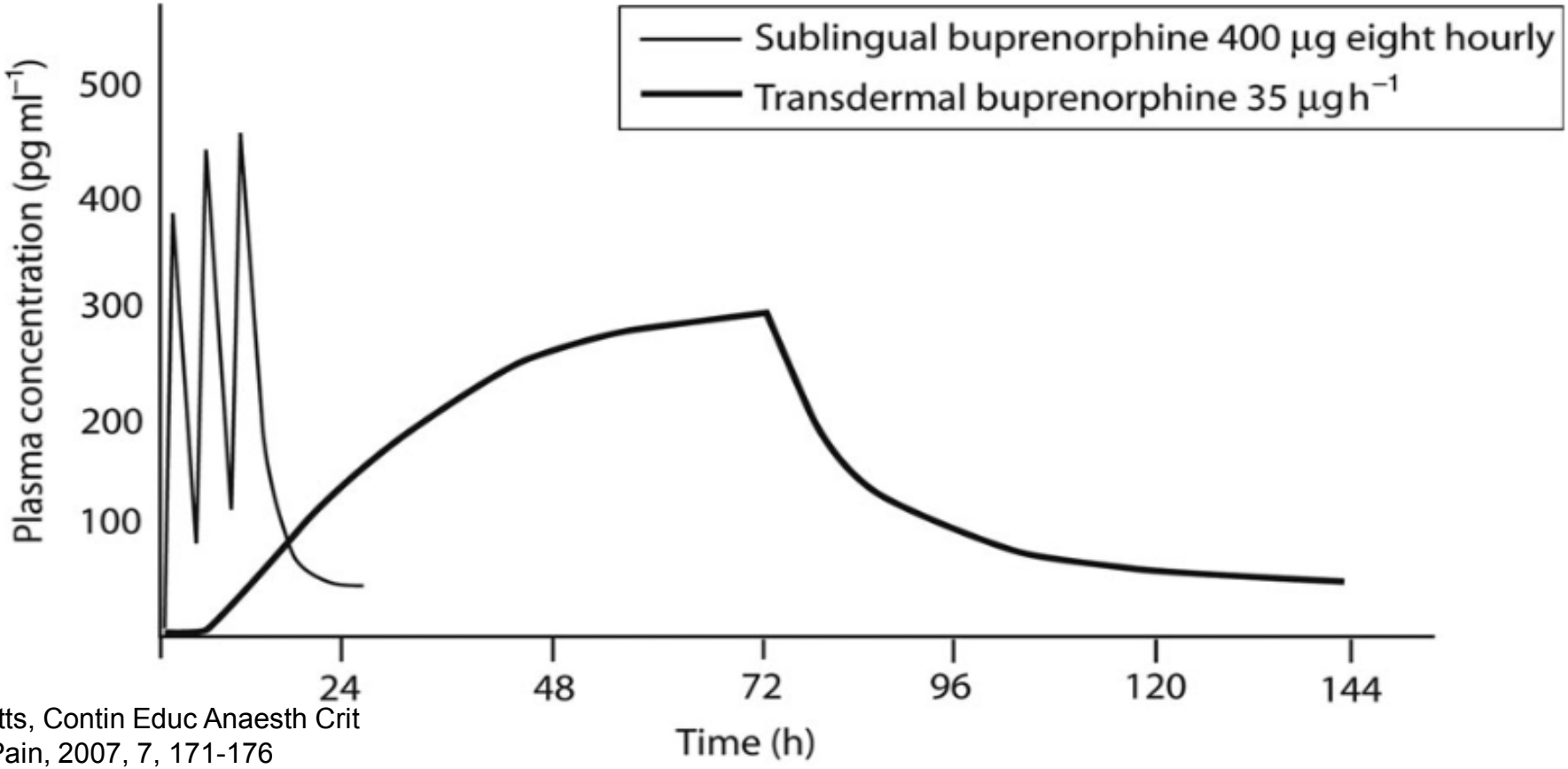
Local effect

- ointments, creams, solutions, patches
- minimal AE
- dermatology

Systemic effect

- transdermal administration
- mainly patches
- continuous release
- local+systemic AE
- high compliance
- easy discontinuation

Comparison of plasma concentrations of buprenorphine after single application of 35 μg h^{-1} patch (removed after 72 h) and sublingual dosing of 400 μg buprenorphine, eight hourly.



Margetts, Contin Educ Anaesth Crit Care Pain, 2007, 7, 171-176

Intranasal administration

- drops, sprays, ointments
- local effect - antiseptics, ATB
  - antihistamines, decongestants
  - antiphlogistics
- systemic effect - analgesics, antivirotics
  - hormones (ADH, gonadotropin, insulin)

Inhalation

- gases, aerosols
- systemic effect – general anesthetics
- local effect – antiasthmatics
- fast onset of effect
- minimal presystemic elimination
- administration from spray cans or other instruments (turbohaler, dischaler, nebuliser)

Rectal administration

- suppositories, capsules, tablets, foams, tampones
- alternative for peroral administration in case of nausea/vomitting or unconciousness
- variable drug absorption

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Sublingual administration

- fast onset of effect
- oinly for small and lipiphilic molecules
- sprays, tablets, dispergable films
- analgesics – fentanyl, buprenorfin
- hypnotics – zolpidem
- vazodilators – nitroglycerine
- antiemetics – ondansetrone
- homeopatics, alergens, cannabis….

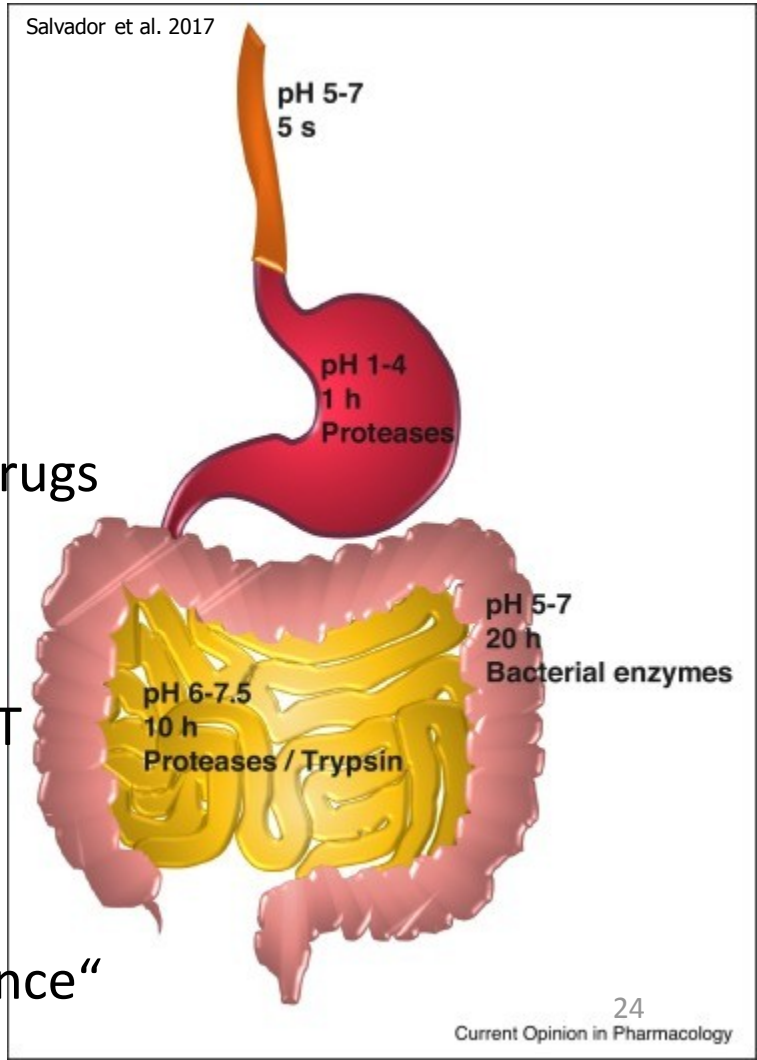
Oral administration

1. for local effect

- minimal AE
- risk of interaction with coadministered drugs
- antacids, laxatives, antibiotics

2. for systemic effect

- drug absorbed from different parts of GIT
    - can be influenced by DDF
- „slow“ effect onset
- the effect depends on patients „compliance“



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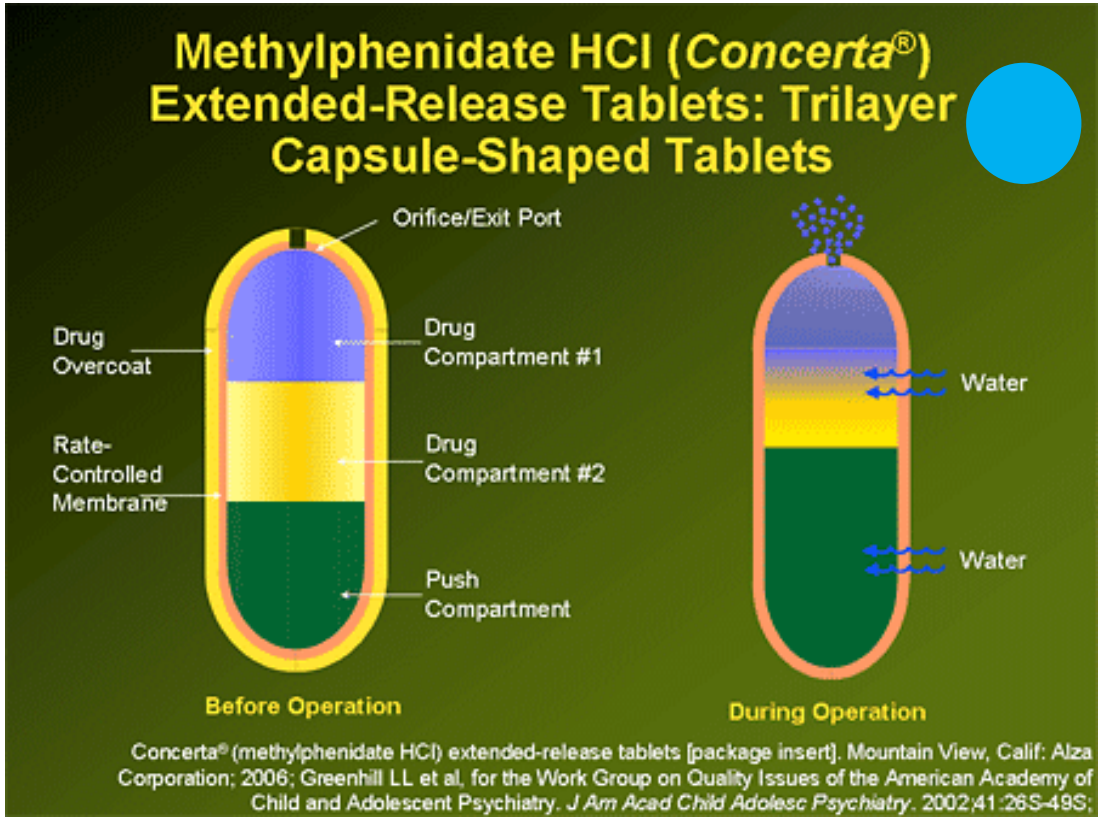
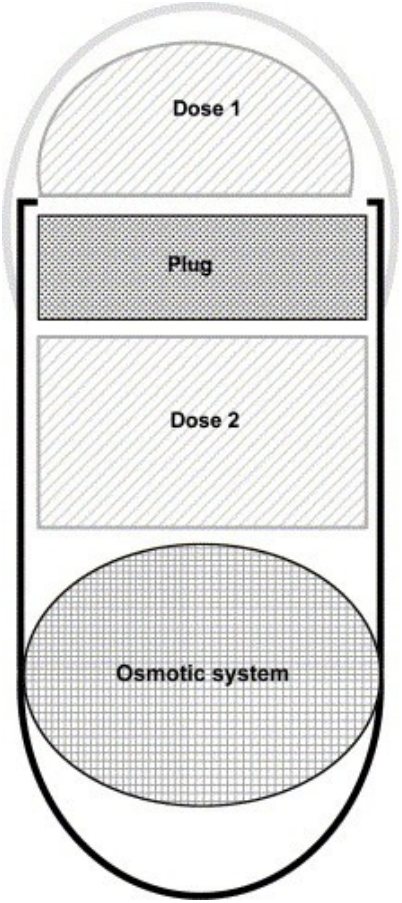
Perorální lékové formy s řízením uvolňováním

- systems of controlled release: matrix
  reservoirs
  particles
  nanoparticles
- controlled release: continuous
  pulsatile





Lobenberg et al, Eur J Pharmaceut Biopharmaceut , 60 2005

Injections

intravenous, intraarterial

- injection/infusion
- 100% bioavailability, „immediate“ effect
- true solutions + emulsions

intramuscular

- max. volume 5 ml
- to *m. glu. maximus*
- absorption: solution> emulsion> suspension

subcutaneous

- to 2 ml
- variable absorption with regard to adipose tissue

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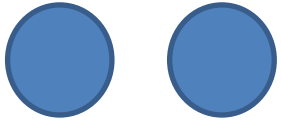
Injections

intradermal

- minimal volume
- diagnostic purposes

intraosseal

- alternative to i.v.
- injection/infusion



- Eg. Atropine onset of the effect
- i.v. 30-90 s; s.c. 15-30 min; i.m. 30-45 min

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Implants

- degradable/nondegradable
- usually s.c. or intraocular
- systemic/local effect
- continuous/pulsatile release = continuous/repeated drug administration
- increased patient‘s compliance
- complicated discontinuation

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Factors influencing the drug delivery approach

- drug physicochemical properties
- therapeutic indication + disease severity
- benefit:risk ratio
- co-morbidities, co-medications

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Innovations in drug administration

- new posssibilities of administration routes are probably depleted => modification of DDF
- the goals are:
    1. increase of drug safety/decrease of drug toxicity
    2. increase the efficacy of administered dose
    3. increase the patient‘s compliance