# BASICS OF BIOPHARMACY

# LADME(R) - TOX SYSTEM

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# Written Test Dates

- 1. September 26
- 2. November 7

---------- above 60,1% in average

- 3. December 5 (above 60,1 %)
- 4. Last chance: written or oral (above 60,1%)

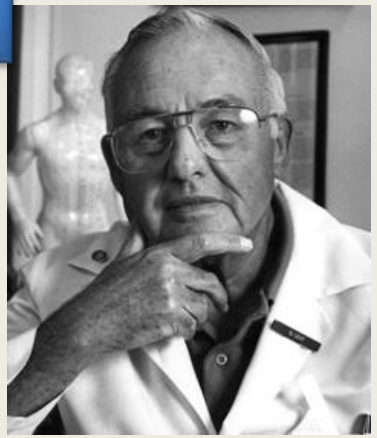
Absences: 3 absences are allowed

# Frequently asked questions in a pharmacy

- How to take the medicine?
- Is the medicine safe for pregnant women?
- Is the medicine safe for nursing women?
- When is it expected to take its effect?
- How long does the effect last?

# What is biopharmacy?

# Development of biopharmacy



Gerhard Levy

Expression „*biopharmaceutics”* was composed By Gerhard Levy and it was written down by *John G. Wagner* in a publication from 1961 for the first time.

Knowledge accumulated from the field of biopharmacy reached a level which was able to be functionable as a separate discipline. *Wagner* later declared the birth of the biopharmacy as: *„a body of knowledge which needed a name”*

Wagner, J.G.: Biopharmaceutics: Absorption aspects, J. Pharm. Sci., 50, p 359-387. 1961.

# What is biopharmacy?

Biopharmacy is a pharmaceutical discipline which could be used by the modern drug discovery, quality control and pharmaceutical attendance.

**Biopharmacy investigates the connection between the medicine and the living organism.**

# Development of biopharmacy

Investigates the characteristics and behaviour of the API and the medicine in the human body.

Biopharmaceutics:

-models the processes accompanying the interactions of the medicine and the human body

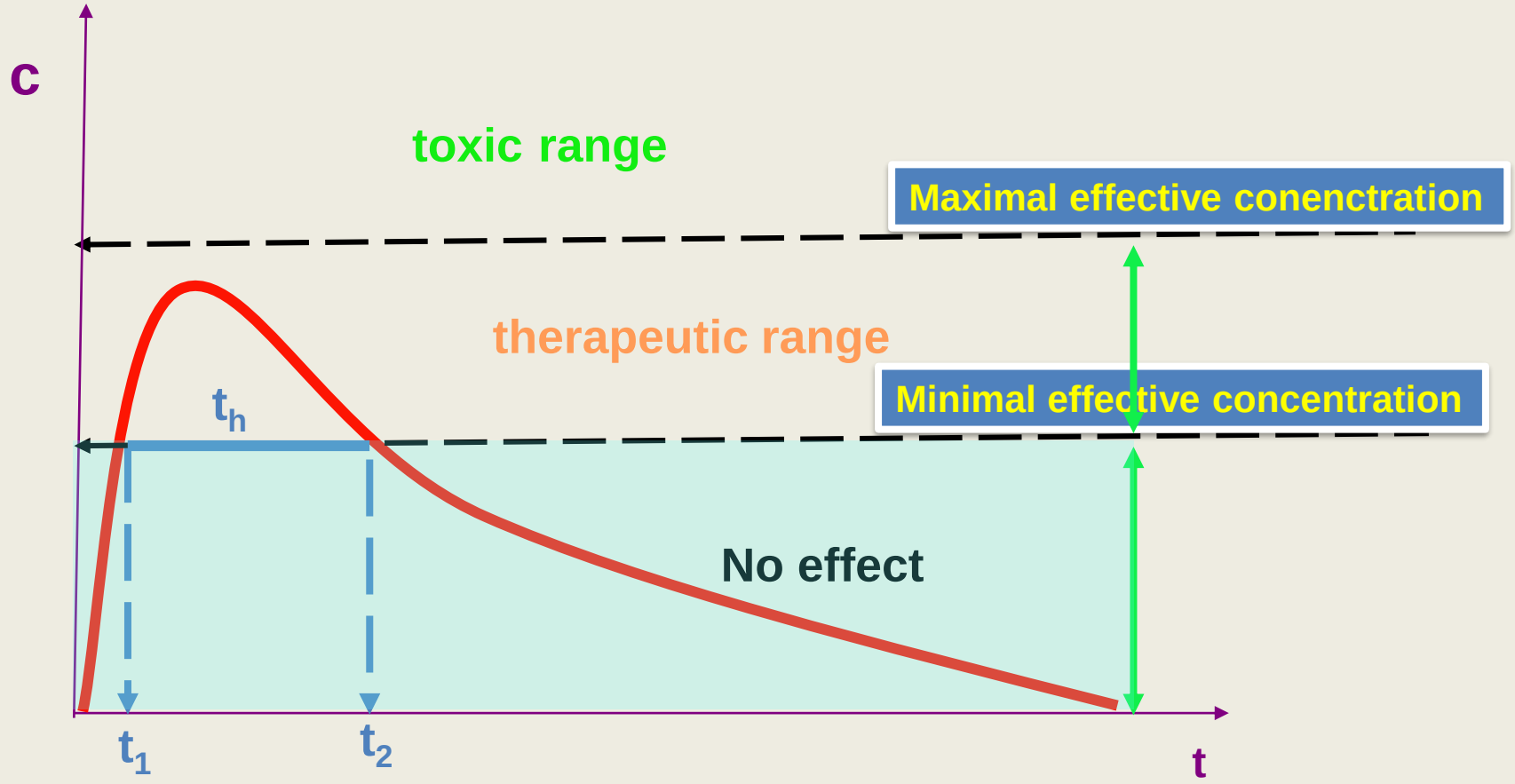
-reveals the main physical, chemical and pharmacological characteristics of the medicines

- examines the pharmacodynamic and/or toxicologic reactions of the human body and the development of the effect

# What are we going to discuss on these lectures?

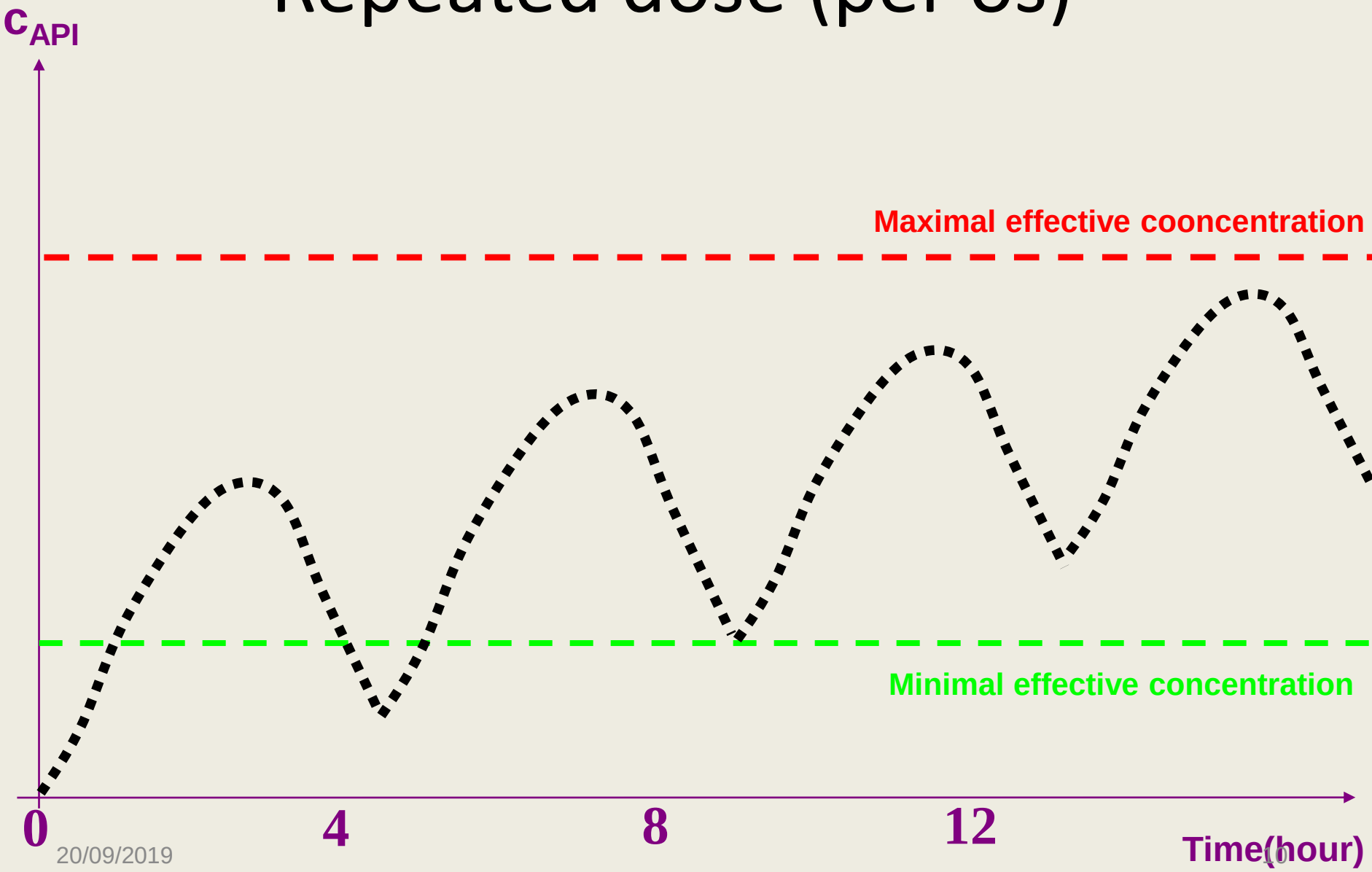
- Behaviour of the medicine in the human body
- Physico-chemical properties of APIs that affect the bioavailability.
- Biopharmaceutical examinations

- Effective concentration and duration of action ($t_h$)

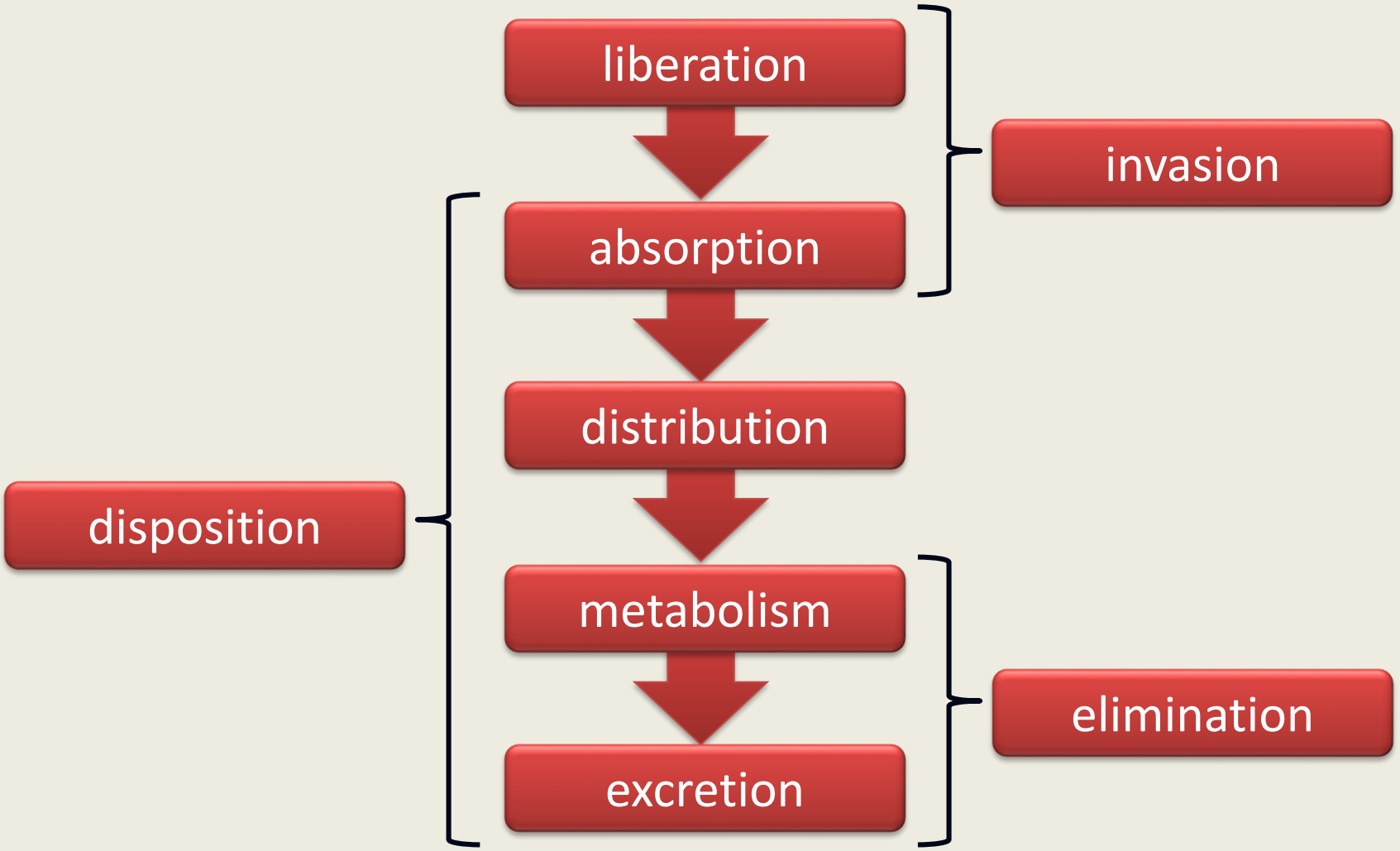



$$t_h = t_2 - t_1$$

# Repeated dose (per os)



# LADME system



# Liberation

**Liberation means the relase of the API from the dosage form.**

# Everything dates back to 1897…

Arthur Amos Noyes

Willis Rodney Whitney

# THE RATE OF SOLUTION OF SOLID SUBSTANCES IN THEIR OWN SOLUTIONS.

BY ARTHUR A. NOYES AND WILLIS R. WHITNEY.

Received October 11, 1897.

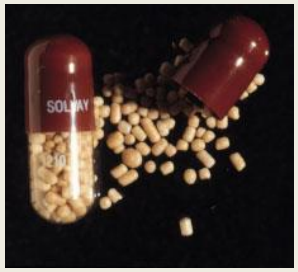
This is then the law which is first to be tested. Its mathematical expression is:

$$\frac{dx}{dt} = C(S - x),$$

where $S$ represents the solubility of the substance, or the concentration of its saturated solution; $x$ the concentration at the expiration of the time $t$, and $C$ a constant.

As this is the case with two substances of so widely different chemical nature and physical properties as benzoic acid and lead chloride, it is safe to assume that the law is a general one. It may be expressed as follows: The rate at which a solid substance dissolves in its own solution is proportional to the difference between the concentration of that solution and the concentration of the saturated solution.

MASSACHUSETTS INSTITUTE OF TECHNOLOGY,
BOSTON, MAY, 1897.




Intestinosolvent coated granules


Capsule containing a tablet with three layers


Coated tablet with immediate effect. Inner matrix releases the API slowly


Osmotic tablet with zero order kinetics


Matrix tablet with controlled release

Tablet composed by compressed micropellets


30 db
Betaloc® ZOK
retard tabletta
50 mg
Hatóanyag:
47,5 mg metoprolol-szukcinát
(megfelel 50 mg metoprolol-
tartarátnak) retard tablettánként
AstraZeneca


60
PREDUCTAL
MR


KÁLIUM-R tabletta
30 db
VALEANT


IBSA
Flector® EP gél
diclofenac epolamin
60 g


KRKA
500 mg
Fromilid uno
500 mg retard filmtabletta
Clarithromycin
7 db


2 db
Sumamed® S
500 mg filmtabletta
500 mg


Augmentin DUO
625 mg filmtabletta
14 db
625 mg
GlaxoSmithKline


30 db
Apo-Famotidin
20 mg filmtabletta

# Absorption

**The API enters the systemic circulation**

- There is no absorption at iv. medicines
- There are several factors affecting the absorption at per os administration

# Distribution

**API(s) enter the tissues from the systemic circulation**

- APIs are usually distributed unequally between different tissues, they can accumulate in different organs
  - ie. Penicillin cannot enter through the blood-brain barrier

# Metabolism

**Biotransformation of the API**

- Medicines are xenobiotics (foreign material) for the human body
- Decreases or terminates the effect of the drug
- On the contrary it can accelerate the effect

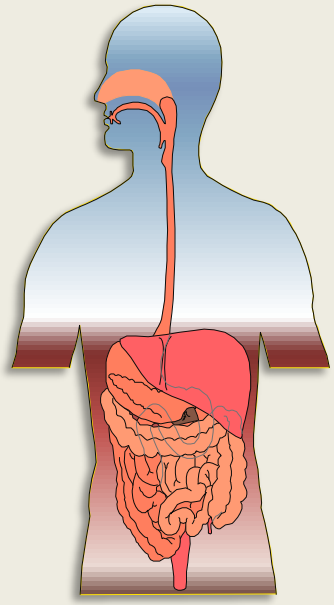
# Excretion

**Terminal disposal of the API or its decayed forms**

- Kidney
- Bile
- Lungs
- Any humour

# Biopharmacy based Pharm. Technology

Aim is to produce a preparation which is able to release the API at the proper…

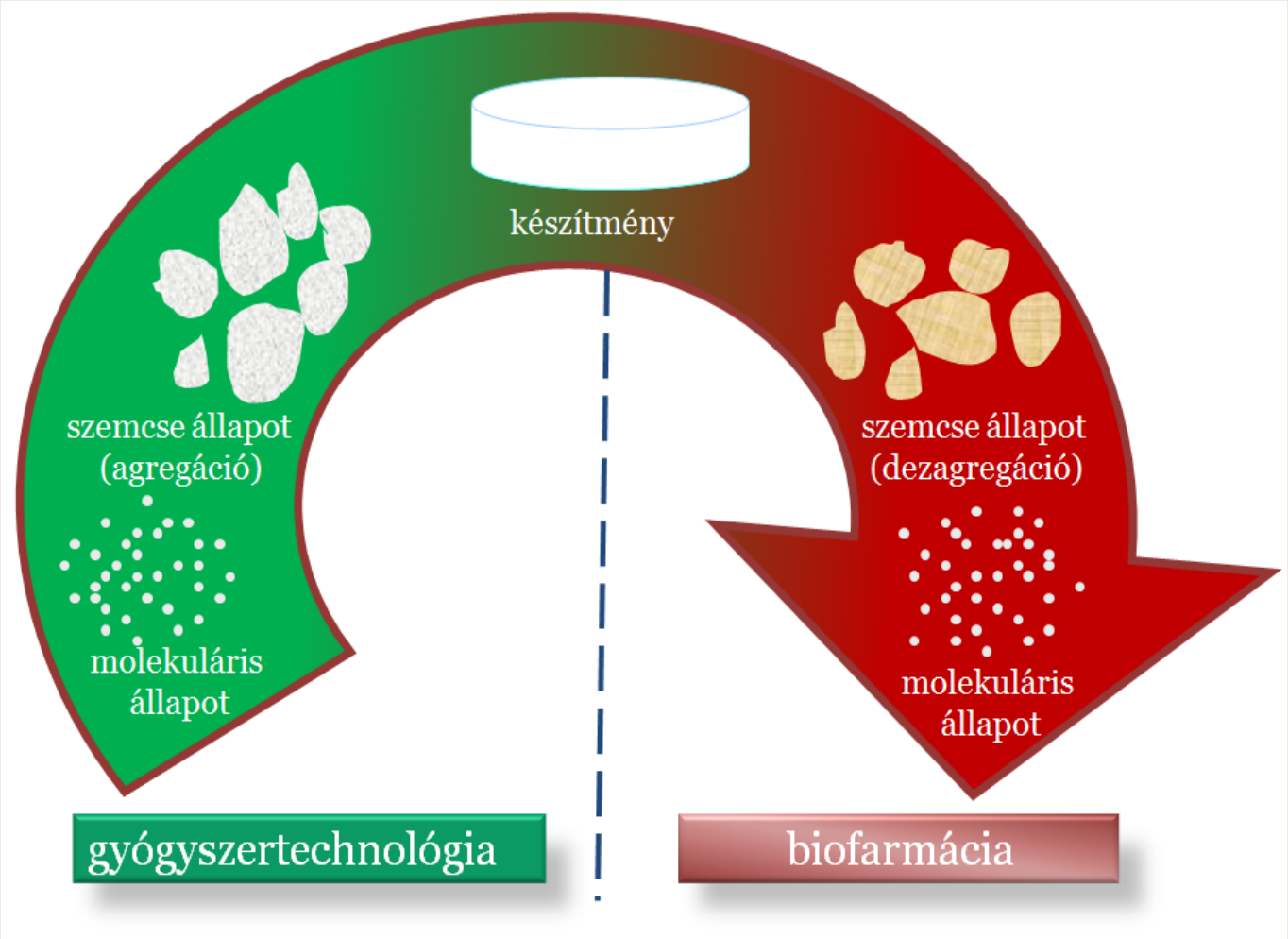


- **- site of action,**
- **- amount (concentration),**
- **- release rate**

**In order to suit these rerquirements, it is important to get acquanted with the biopharmaceutical characteristics of the medicine.**

Biopharmaceutical basics

# Dual characteristics of the medicine



# Fate of drug administered

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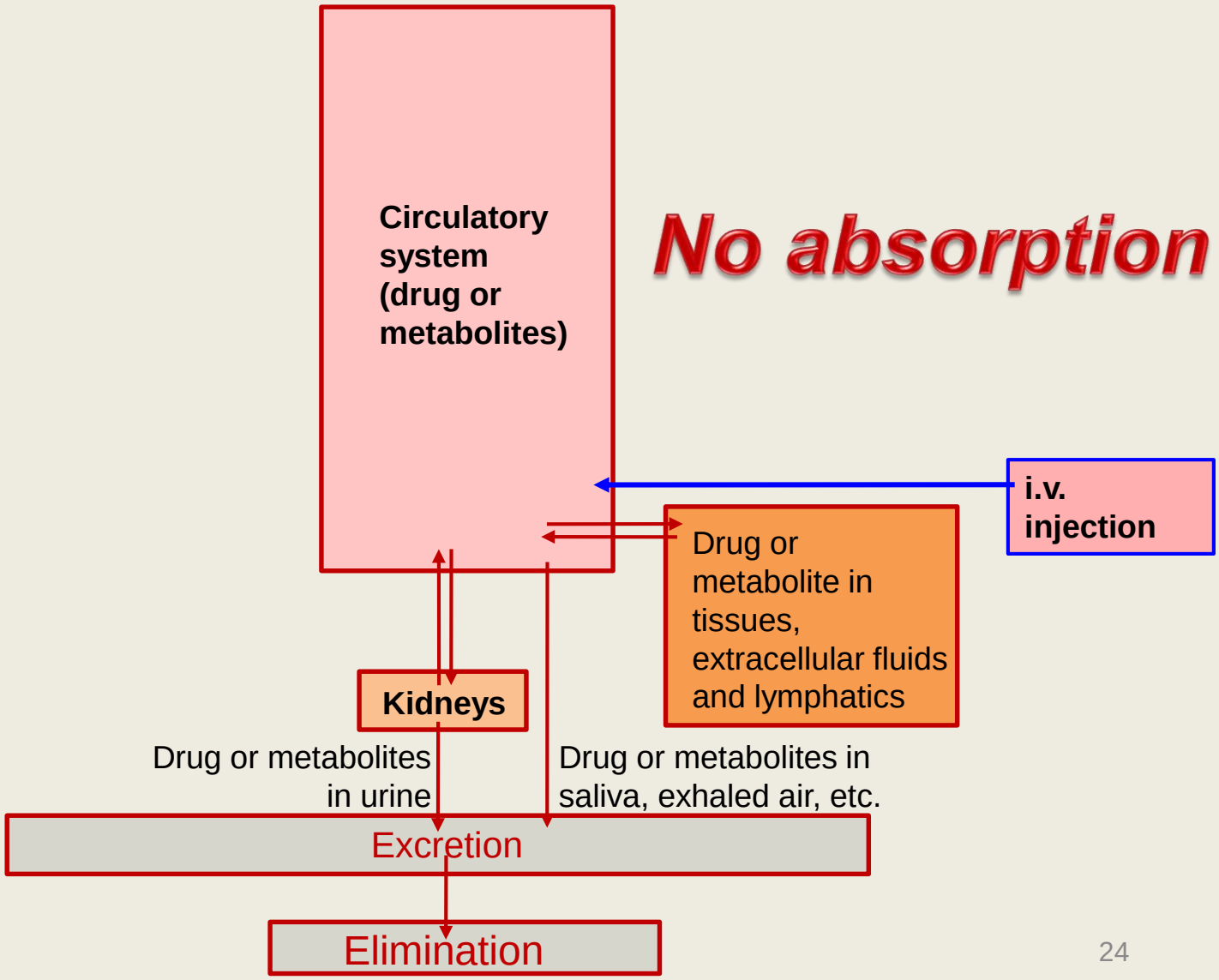

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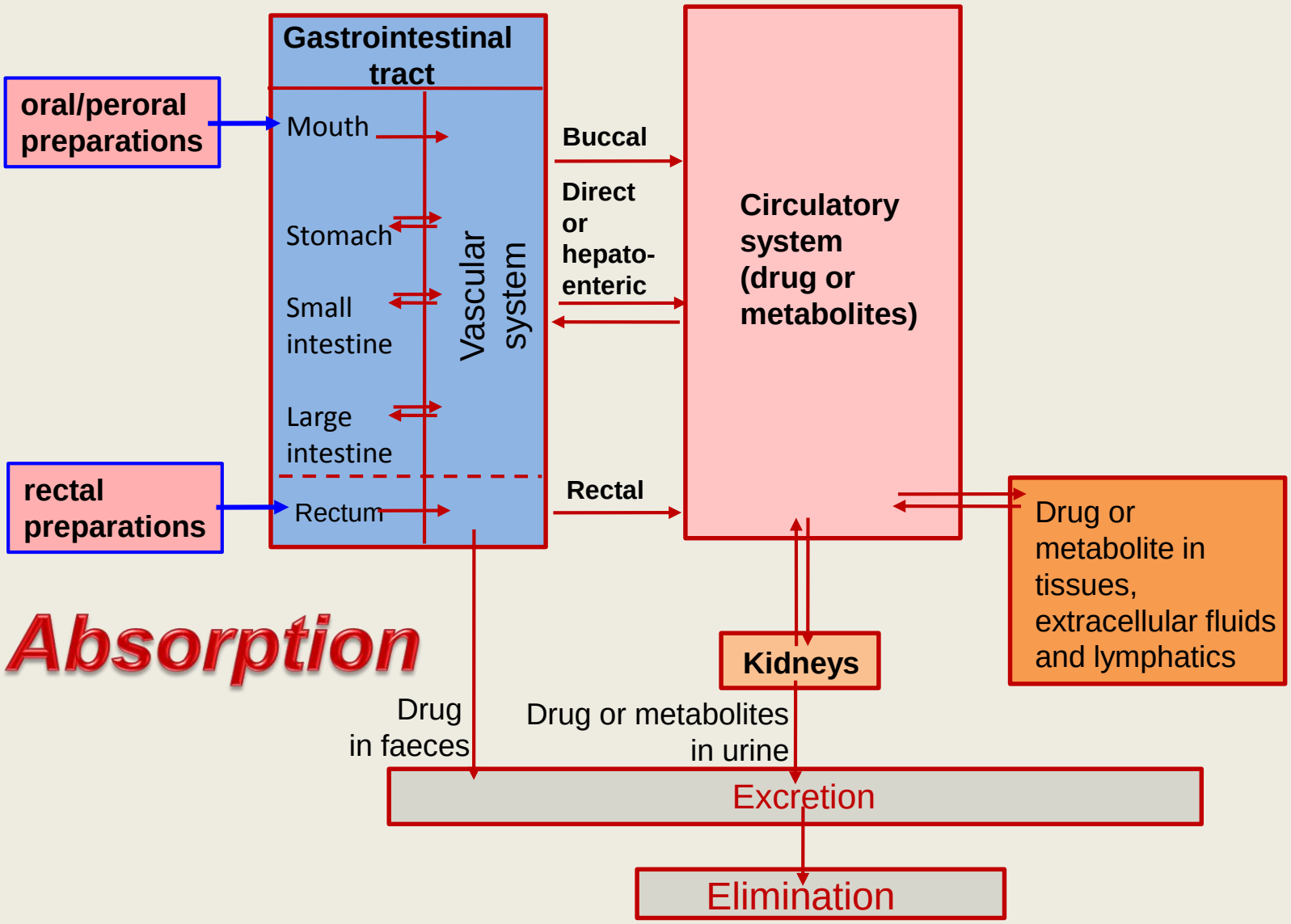

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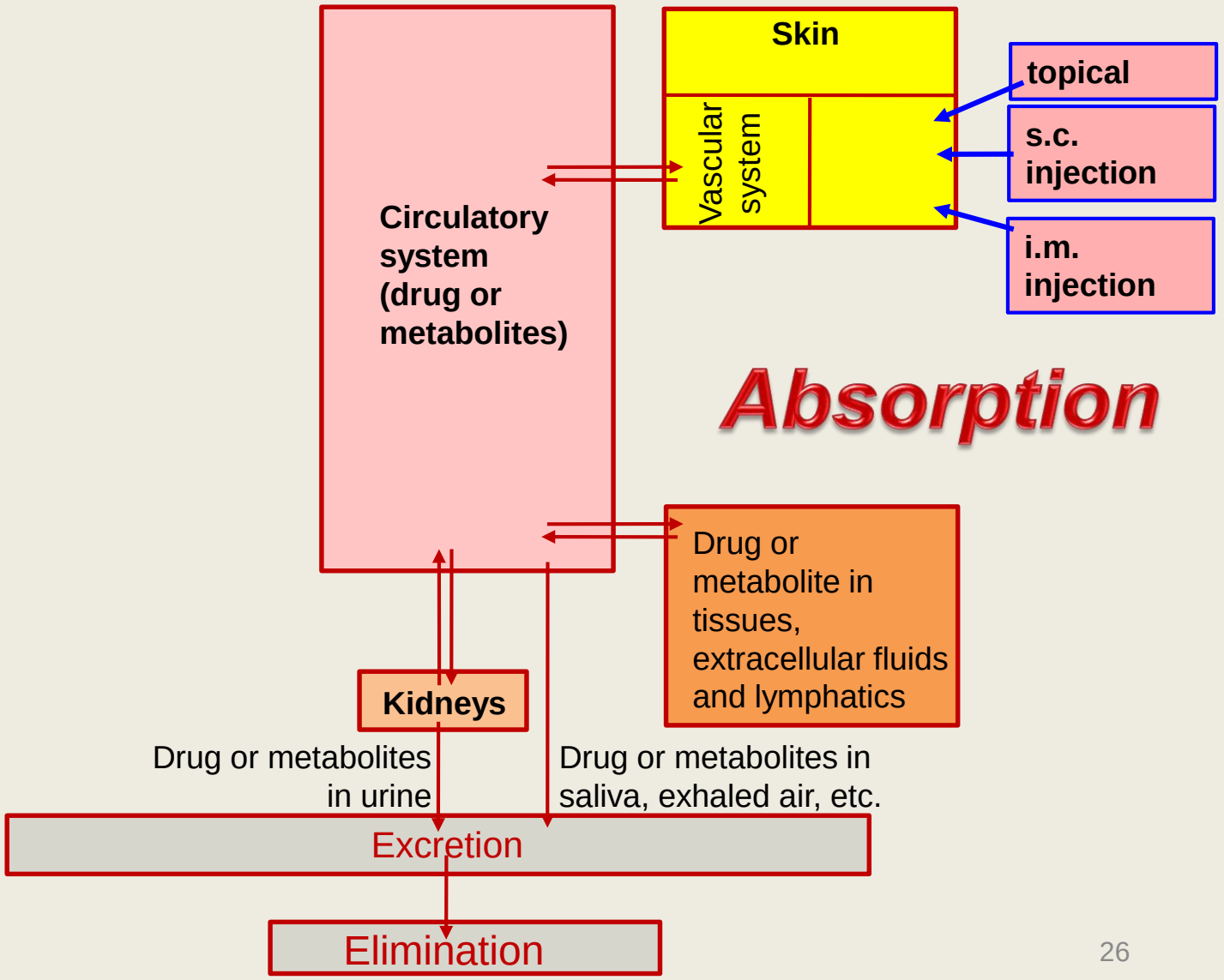

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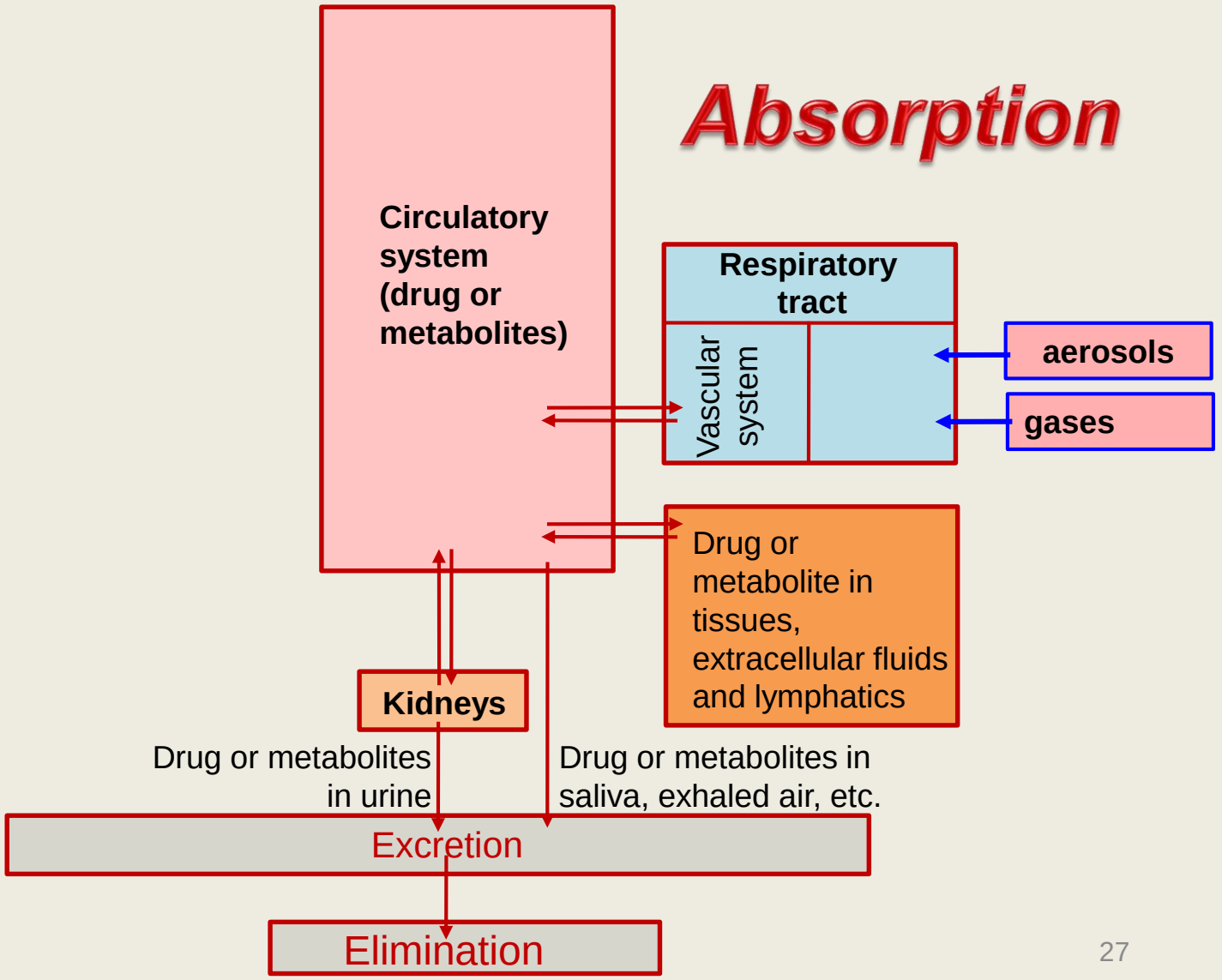

# Routes of administration

The choice of the administration route may be influenced by

1. ease of administration,
2. quantity of drug to be administered
3. site of therapeutic action,
4. desired onset of action,
5. desired duration of action,
6. characteristics of metabolism and excretion,
7. toxicity

# Routes of administration

## 1. Ease of administration

- Status of the patient:
  - some patients are unable to swallow
  - Babys or elderly might have difficulty with swallowing
  - avoid solid, oral dosage forms and prefer liquid dosage forms or non-oral routes of administration
  - oral route of administration is inadvisable for a patient experiencing nausea and vomiting

# Routes of administration

## 1. Ease of administration

- Physico-chemical characteristics of the API:
  - Severel substances are broken down by gastric acid (some penicillins, peptide hormones like insulin)

- Patient complience
  - The most comfortable route of drug administration for the patient is the oral administration

# Routes of administration

## 2. Quantity of Drug

- Sometimes route of administration is chosen taking into account the amount of a drug
  - a tablet containing a lot of filler (diluent) might be preferred for a drug containing a very small amount of active ingredient
- iv. infusion is an excellent method for systemic delivery of large quantities of medication
  - rapidly diluted in the bloodstream
- iv. injections and infusions can deliver a higher dose of medication to the target site
  - important in serious illnesses

# Routes of administration

## 3. Site of the therapeutic action

- Choice of the administration route is influenced by the desired site of action
- The term ***local use*** refers to site-specific applications of drugs (creams, pachtes, inhaled preparations etc.)
- In the case of ***systemic use*** the drug should be absorbed into the blood and transported throughout the body, therefore:
  - the status of the patient (liver- or kidney deseases)
  - bioavailability of the drug

  are very important.

# Routes of administration

## 4. Desired onset of action

**Emergency care:**

- Inhaled products
- Tablets placed under the tongue or between cheek and gums work quickly, because medication bypasses stomach and liver, goes directly into bloodstream
- Drugs injected/infused directly into the bloodstream are carried immediately throughout the body

# Routes of administration

## 4. Desired onset of action

- **Oral medications for systemic use** must proceed through several steps before they evoke their therapeutic effect (desired pharmaceutical action on the body), however:
  - Liquid solutions or suspensions work faster than oral tablets or capsules, because medication is more readily available for absorption
- **Topical medications** work quickly
  - localized therapeutic effects, especially those
    - **applied to the skin**
    - **inhaled into the lungs**
    - **instilled into the eye**

# Variation in time of onset of action for different dosage forms

| Time of onset of action | Dosage forms |
|---|---|
| **Seconds** | i.v. injections |
| **Minutes** | i.m. and s.c. injections, buccal tablets, aerosols, gases |
| **Minutes to hours** | Short-term depot injections, solutions, suspensions, powders, granules, capsules, tablets, modified-release tablets |
| **Several hours** | Enteric-coated formulations |
| **Days to weeks** | Depot injections, implants |
| **Varies** | Topical preparations |

# Routes of administration

## 5. Desired duration of action

- The ***duration of action*** is the length of time the drug produces the desired pharmacological effect
  - Controlled- /extended-release tablet may last for 12 to 24 hours compared with 4 to 6 hours for same drug in immediate-release formulation
  - Transdermal patches deliver small amount of a drug steadily over many hours or even days
  - Sustained-duration effect can be achieved by administration of intravenous (iv.) infusion
  - Injections into the muscle and skin last longer than injections directly into the bloodstream

# Routes of administration

## 6. Characteristics of metabolism and excretion

- Liver metabolism breaks down the active drug to inactive metabolites for elimination, therefore prevents drug accumulation and toxicity.
- ***First-pass effect*** means, that the drug is metabolized by the liver before reaching systemic circulation
  - such drugs should be given in larger oral doses or by another route of administration to bypass or overcome metabolism by the liver

# Routes of administration

## 6. Characteristics of metabolism and excration

- Age-related or disease-related changes in liver or kidney function can cause:
  - drug accumulation
  - toxicity
- Older patients should be often prescribed lower doses of medication
- If patients are on multiple potent prescription drugs, there is a risk of a drug-drug interaction
  - drug accumulation
  - toxic blood levels increases

# Routes of administration

## 7. Toxicity

- ***Toxicology*** is the science that deals with the toxic effects of drugs or other substances in the body
- Physicians must weigh therapeutic benefit against the risk of toxicity
- Some drugs have narrow therapeutic-toxic index called the “therapeutic window”
  - very little difference exists in the therapeutic versus toxic blood level
  - laboratory drug levels are ordered if the physician suspects toxicity
- Toxicity of a drug may affect route of administration

# Administration

1. **Enteral**
   - Oral
   - Peroral
   - Rectal
2. **Parenteral**
   - Injections, infusions
3. **Topical**
   - Nasal
   - Eye preparations
   - Ear preparations
   - Vaginal preparations
   - Inhaled preparations
   - Transdermal patches

# Locations, methods and dosage forms

| location | method | dosage form |
|---|---|---|
| vein | ***intravenal*** | injectable solution |
| artery | ***intraarterial*** | injectable solution |
| heart | ***intracardial*** | injectable solution |
| epidural | ***epidural*** | injectable solution |
| joints | ***intraarticular*** | injectable solution |
| muscle | ***intramuscular*** | injectable solution, emulsion, suspension |
| skin | ***intracutaneous*** | injectable solution |
| subcutaneous connective tissue | ***subcutaneous*** | injectable solution, suspension |
| rectum | ***rectal*** | suppository, enema |
| abdominal cavity | ***intraperitoneal*** | solution, suspension |
| skin | ***epicutaneous*** | solution, emulsion, suspension, |
| trought the skin | ***transdermal*** | patch, ointment |
| bronchi and alveoli | ***inhalation*** | aerosol, spray |
| conjuctiva | ***conjuctival*** | solution, suspension, emulsion (eye drop), „oculentum” |
| vagina | ***vaginal*** | vaginal tablet, „globulus”, suppository, „ovulum” |

# FAQ

- What does the pharmacist offer?
- Which preparation is better? (Liberation)
- When and how to take? (Absorption)
- What about pregnant women? (Distribution)
- What about nursing women? (Excretion)
- Time of action? (Entering the API into the blood)
- Duration of action? (Depends on the dosage form)

# Thank you for your attention!