Pharmacokinetics and drug bioavailability

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Learning objectives

- Understand what is meant by pharmacokinetics
- Be able to define bioavailability
- Be able to describe factors that affect drug bioavailability, for both biological (patient-specific) and chemical (drug-specific) factors

Pharmacokinetics:
The journey of a drug through the body

To achieve its effect a drug must first be presented in a suitable formulation at an appropriate site of **ADMINISTRATION** and then (usually) **ABSORBED** and **DISTRIBUTED** through the body to its site of action. For the effect to wear off the drug must almost always be **METABOLISED** and/or **EXCRETED** with these residues being **VOIDED** (**REMOVED**) from the body.

Pharmacokinetics: The journey of a drug through the body (ADME)

ADMINISTRATION

ABSORPTION

DISTRIBUTION

METABOLISM

EXCRETION

REMOVAL

Pharmacokinetics

- **The variation with time of the drug concentration in the blood (or plasma).**
- **There are a number of derived parameters that describe the drug's journey through the body.**

Bioavailability

Proportion of the administered drug that is available within the body to exert its pharmacological effect

Pharmacokinetics

Apparent volume of distribution

The volume in which a drug appears to be distributed

- an indicator of the pattern of distribution

$$V_D = [drug]_{total} / [drug]_{plasma}$$

Low values: high plasma concentration, e.g. because of protein binding

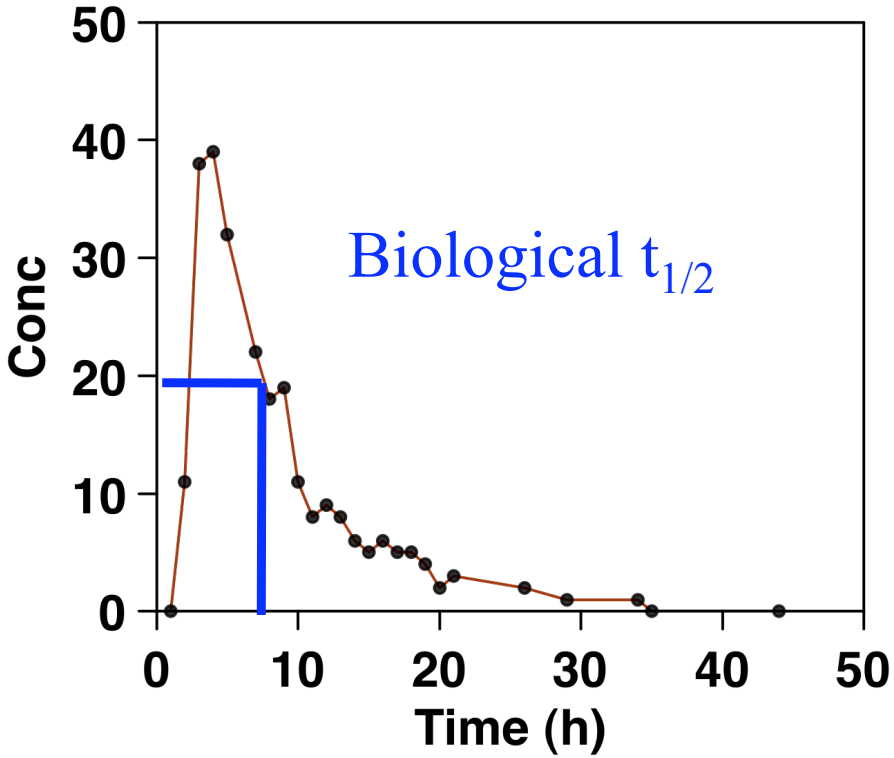
High values: e.g. fat-soluble drug sequestered into lipids

Pharmacokinetics

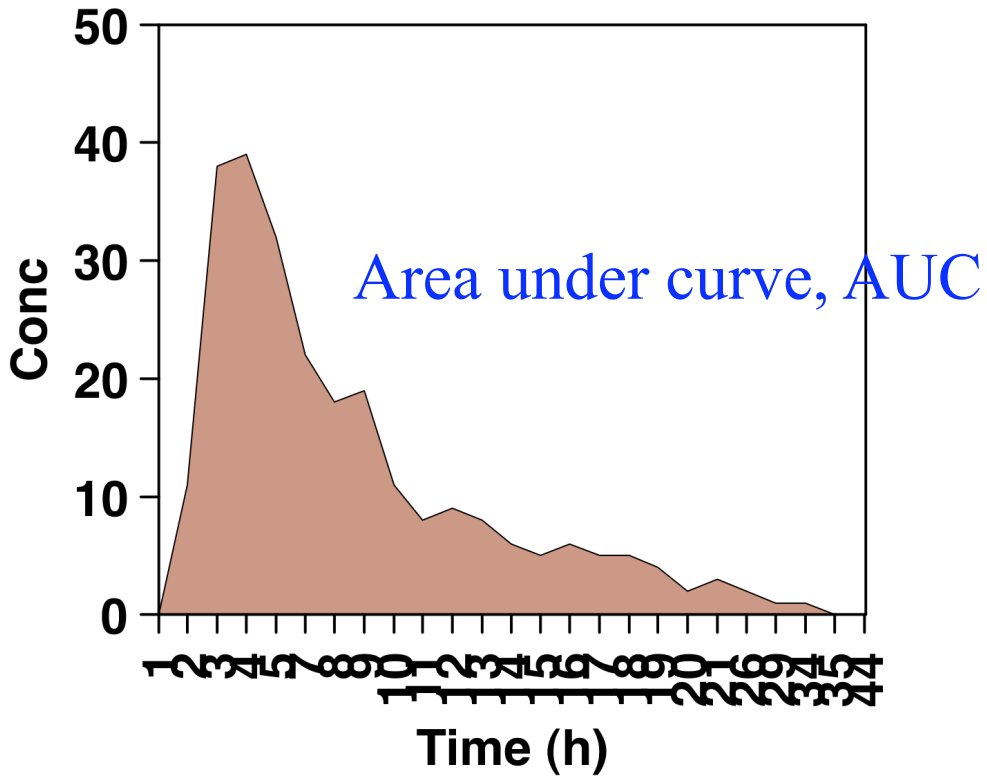
Biological half-life

Time taken for the concentration of drug (in blood/ plasma) to fall to half its original value

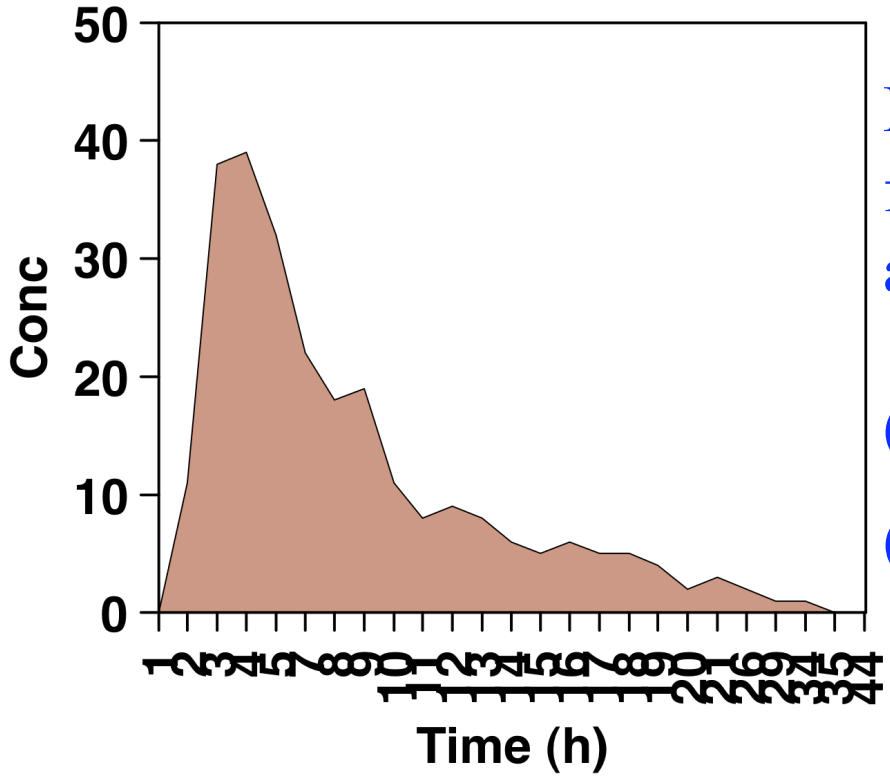
Pharmacokinetics



Pharmacokinetics



Pharmacokinetics



Bioavailability: fraction of drug that is absorbed. F

$$\frac{(AUC_{iv} \times dose_{o})}{(AUC_{o} \times dose_{iv})}$$

Pharmacokinetics:
The journey of a drug through the body

Summary

- To achieve its effect a drug must first be presented in a suitable formulation at an appropriate site of **ADMINISTRATION.**
- The drug is then (usually) **ABSORBED** and **DISTRIBUTED** through the body to its site of action.
- For the effect to wear off the drug must almost always be **METABOLISED** and/or **EXCRETED.**
- Finally the drug residues are **VOIDED** (**REMOVED**) from the body.

Drug Administration

Drug actions may be…

SYSTEMIC - the entire organism

LOCAL – restricted to one area of the organism

Drug administration routes

ENTERAL ROUTES

sublingual, buccal, oral, rectal

PARENTERAL ROUTES

intravenous, intramuscular, subcutaneous, percutaneous, inhalation

Drug Absorption

Drugs have to traverse both aqueous and lipid environment

Lipid soluble drugs (e.g. anaesthetics)

usually small volatile molecules that ‘dissolve’ into membranes

Water soluble drugs (e.g. most drugs)

usually weak acids or bases able to become charged – ionisation depends on pKa of the molecule and the pH of the medium

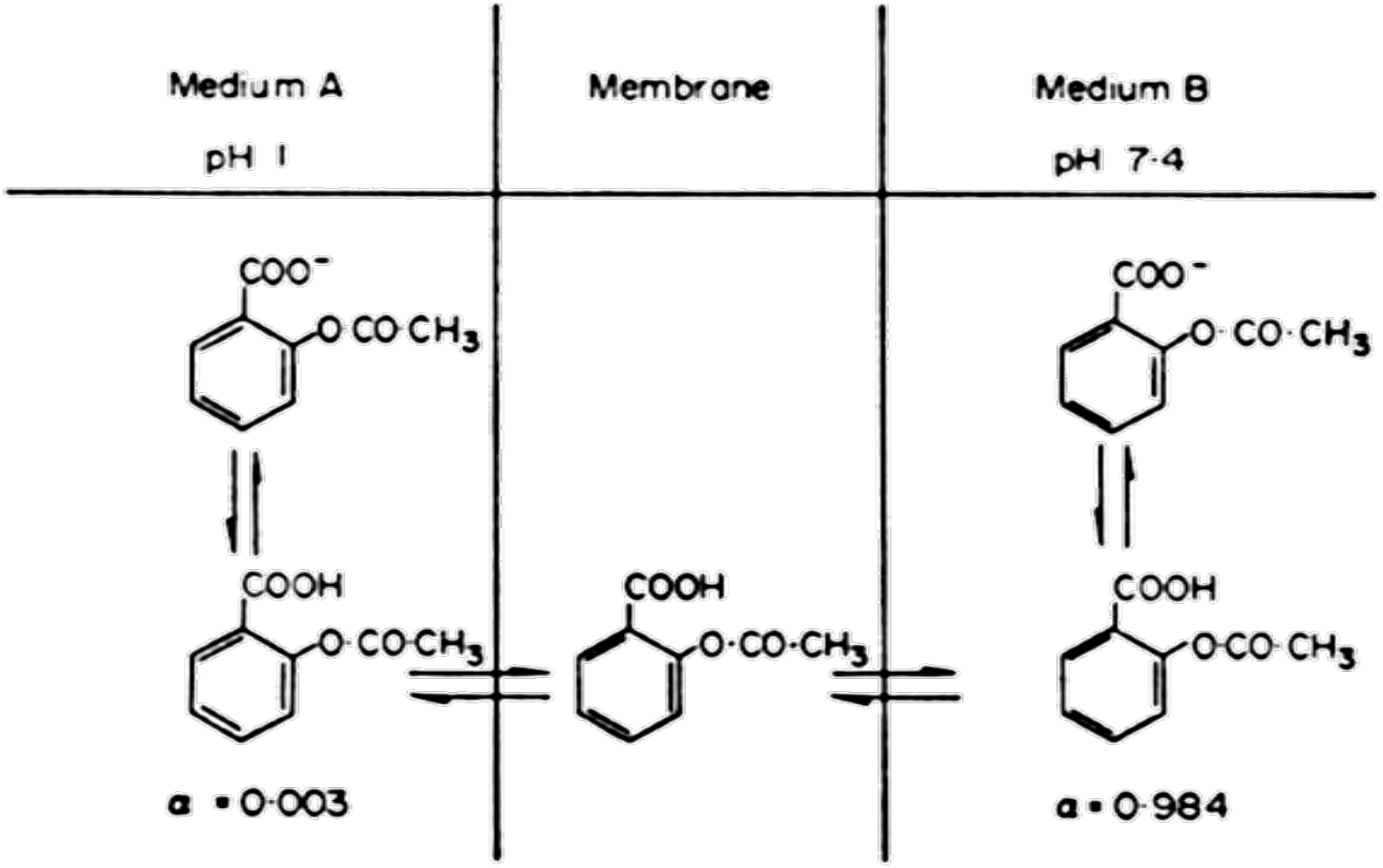
Drug absorption

Transfer across membranes…

- Passive diffusion (most common – pH partition hypothesis)
- Facilitated diffusion
- Active transport (important in drug excretion)
- Pinocytosis (phagocytosis-like mechanism)
- Filtration (small water-soluble molecules)
- Paracellular transport (around cells)

Drug absorption

Passive diffusion – The pH Partition Hypothesis



Effects of lipophilicity

Octanol/water partition coefficient: log K_{ow}, log P

Widely used in quantitative structure-activity relationship (QSAR) modelling

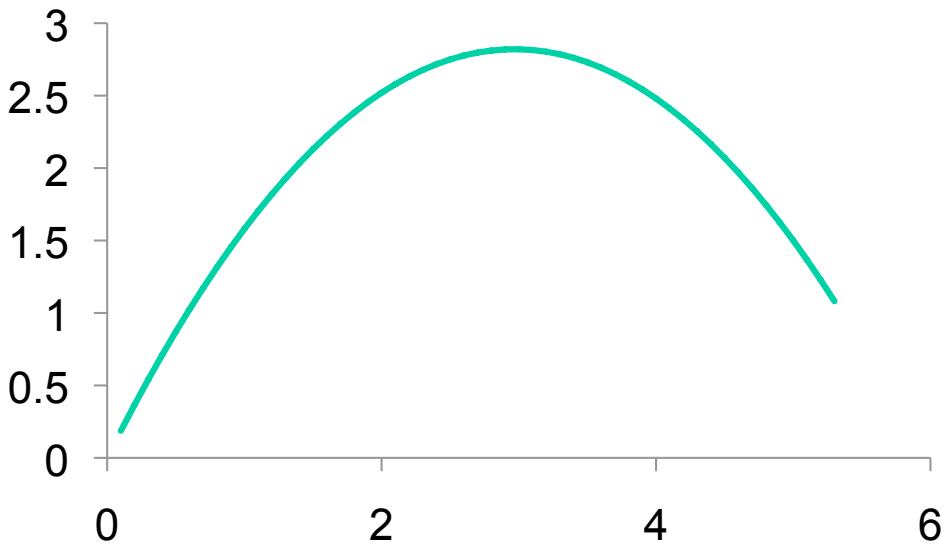
- attempt to predict activity – including uptake
- Uptake dominated by log P term
- Log P can be measured or calculated (based on a fragment principle)

Effects of lipophilicity

Octanol/water partition coefficient: log K_{ow}, log P

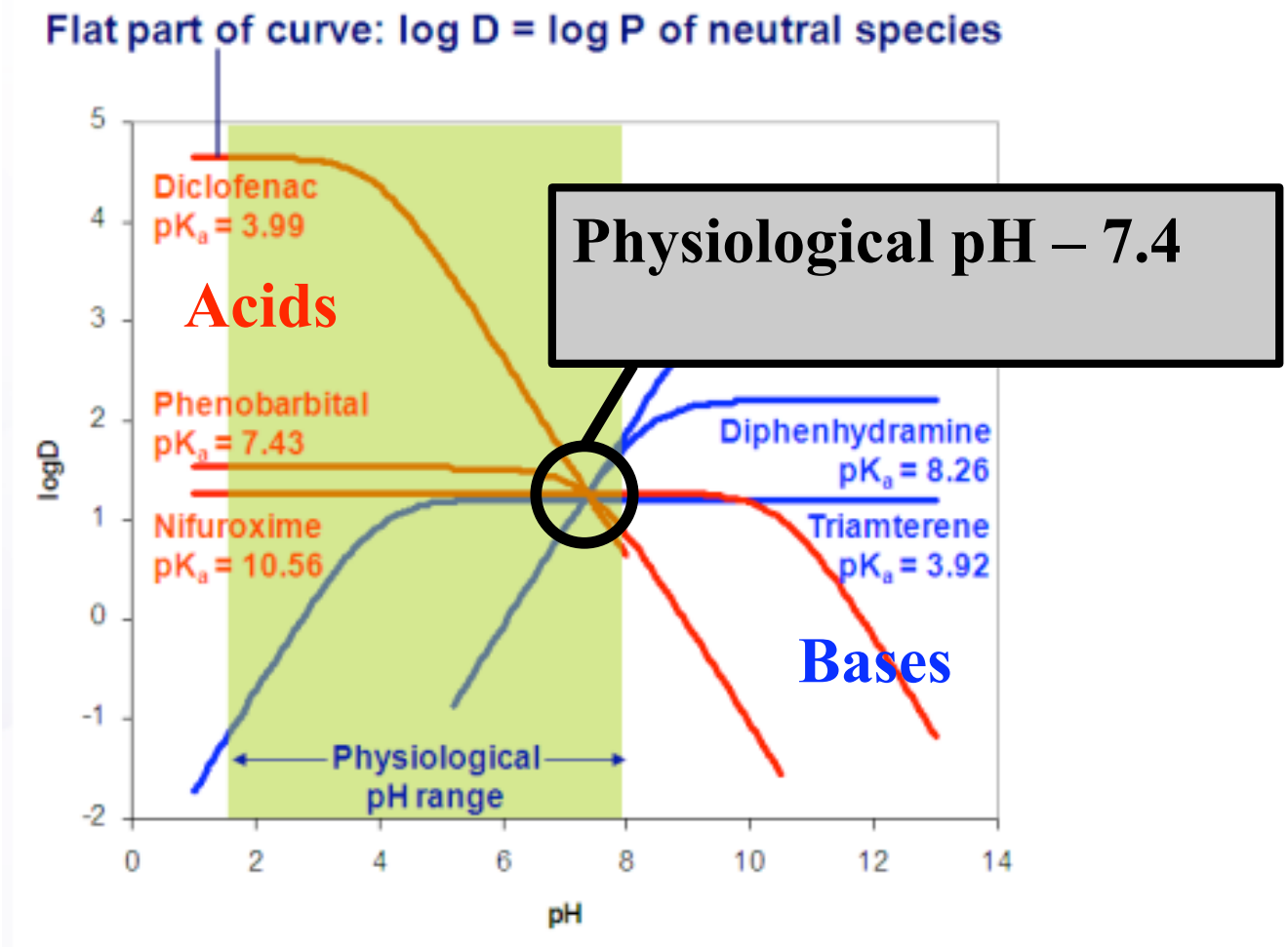
Widely used in quantitative structure-activity relationship (QSAR) modelling

- Gives a non-linear ("quadratic") relationship



Effects of lipophilicity

Log P can be replaced by log D, which takes ionization status into account



An example: aspirin

pK_a is about 3.5.

- what is stomach pH?

Aspirin is essentially near-completely ionized

- Henderson-Hasselbalch equation: $pH = pK_a + \log(A^-/HA)$

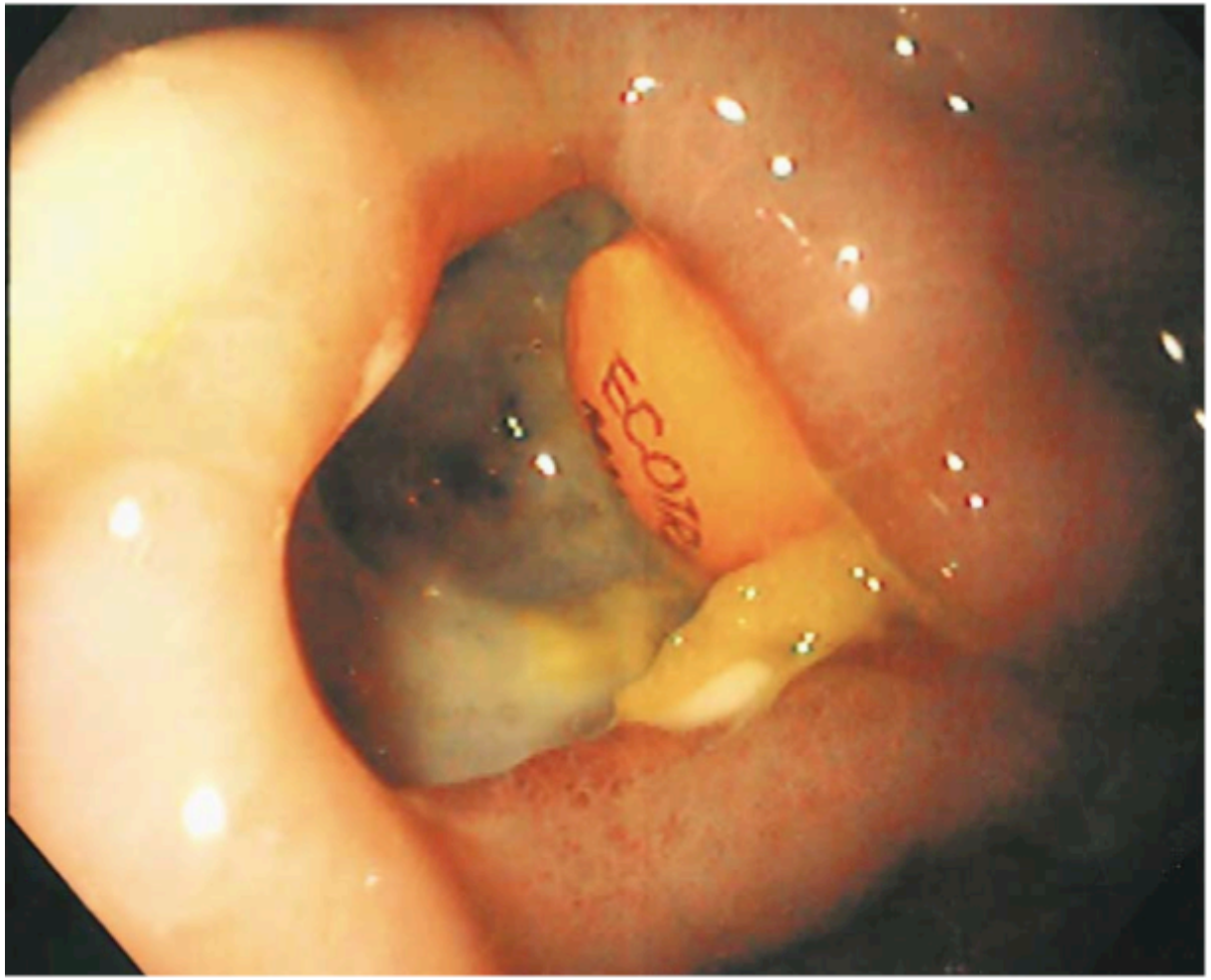
Absorbed in stomach – but transit time is fast!

- When would you use soluble aspirin, and when would you use enteric-coated aspirin?

- Soluble: rapid pain relief; enteric-coated: slow release

N Engl J Med 343:863, September 21, 2000,
Images in Clinical Medicine

An Aspirin Tablet and a Gastric Ulcer



Effects of formulation

Drug formulation – what options are there?

e.g. for oral route: tablets, gelatin capsules, syrup/ tincture

Excipients

– why are they used? For stability, bulk, taste, performance

– what are they? e.g. Solid formulations: sucrose, lactose, talc, chalk, salts.

Liquid formulations: water, alcohol

Drug distribution

Factors influencing drug distribution…

- Regional blood flow
- Extracellular binding (Plasma-protein binding)
- Capillary permeability (tissue alterations – renal, hepatic, brain/CNS, placental)
- Localisation in tissues

Drug excretion

In man there are two major routes of drug excretion…

Kidney

ultimately responsible for the elimination of most drugs

Liver

some drugs are concentrated in the bile (usually large molecular weight conjugates)

What other things affect bioavailability?

- Gastric motility
- Individual differences (pharmacogenomics)
- Diseases of absorption
- Diseases which affect blood flow
- First-pass metabolism

When does a drug not need to be bioavailable?

- Non-systemic (topical) administration – e.g. to GI tract, skin creams, inhalation

- Pro-drugs: require metabolism to be active

Toxicity versus effectiveness

Two very important parameters for a drug:

Therapeutic index and **therapeutic window**

Therapeutic index = TD_{50} / ED_{50}

Therapeutic window: “The range between the lowest dose that has a positive effect, and the highest dose before toxic effects outweigh the therapeutic effect.”

Nutritional bioavailability

Nutritional bioavailability is not defined as strictly as for drug bioavailability – e.g. it may not be possible to carry out i.v. studies

An example: selenium supplements

Why might we want to take selenium? Anti-cancer effects

What governs our natural selenium intake? Soil Se (affects food Se)

What is the active form of selenium in the body? SeCys

What is the commonest form of selenium found in the body? Depends!

What form of selenium is administered in supplements? Very variable

Why is it important to know all this for selenium? 'Therapeutic index' is low – lowest of any mineral

An example: selenium supplements

Nutritional bioavailability is not defined as strictly as for drug bioavailability – not possible to carry out i.v. studies for Se!

- about 70% of studies use total tissue Se levels

- about 10% of studies use stable Se isotope ratios

It is a very complex question, with no consensus answer! But:

- SeMet is more available than inorganic Se
- Methylated Se may be more effective in anti-cancer pathways