Pharmacokinetics

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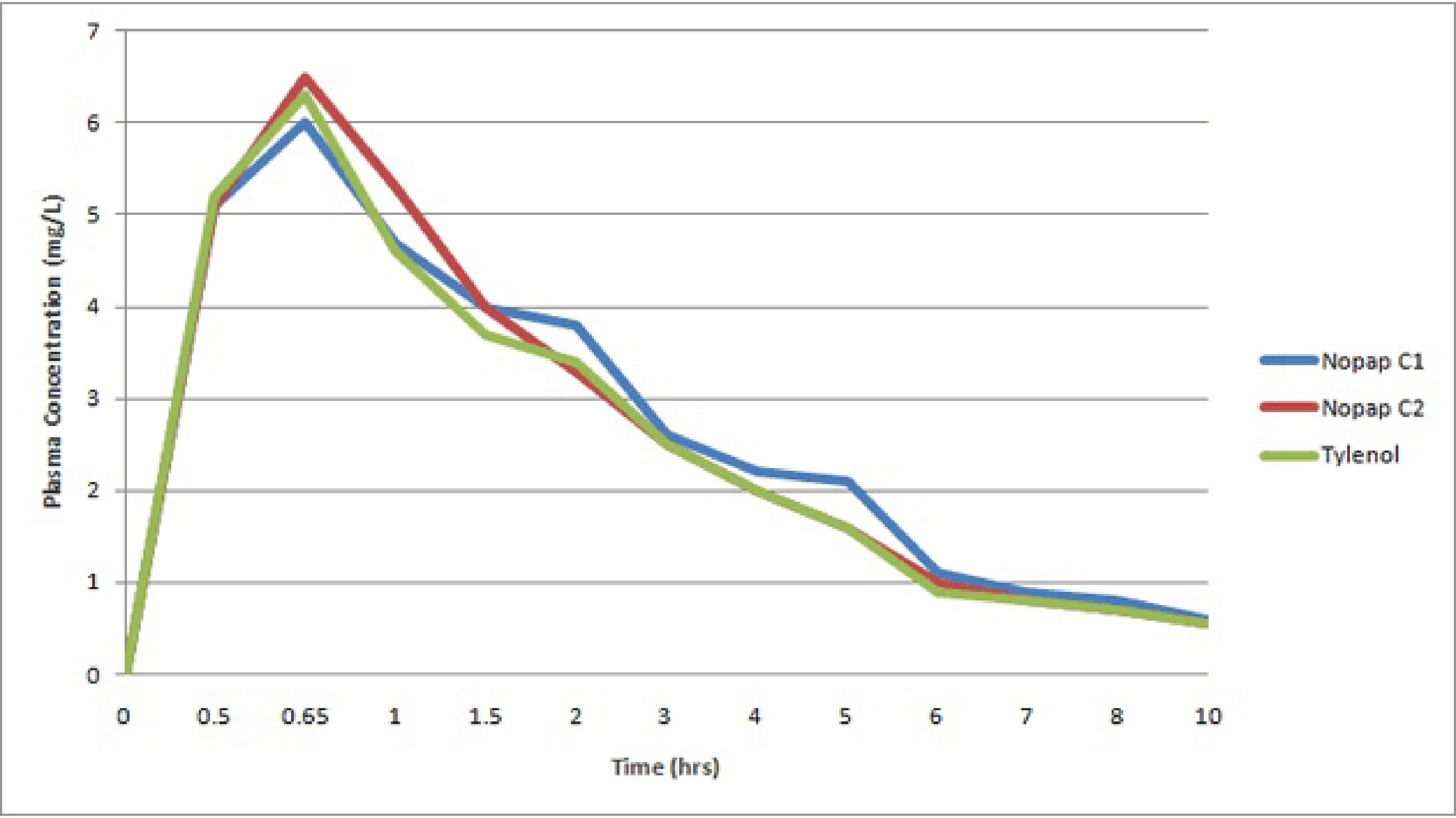
Bioequivalence



- **Drug products are considered to be *bioequivalent* when the rates and extents of bioavailability of the active ingredient in the two products are not significantly different under suitable test conditions**

Binding

- Usually, after absorption, drugs bind to proteins.
- Bound drugs are larger molecules, and therefore can not distribute well and considered as the depot inactive forms of the drug.
- A balance is created between bound (inactive) and unbound (active) forms of the drug.
- Binding can cause drug interactions.

DRUG BINDING TO PLASMA ALBUMIN

- Some drugs bind nonspecifically and reversible to various plasma protein, albumin and globulins, in which the bound and free drug reach equilibrium, and only the free drug exerts a biological effect.

- In general albumin binding reduces pharmacological activity but prolongs duration of action in a way dependent on affinity, binding capacity and rate of dissociation.

- Drug interactions occur on albumin by the displacement of one drug by another. Can raise dose of some drugs to toxic levels.

- For example Anticoagulants (Warfarin) can be displaced by the anti-inflammatory agents Phenylbutazone.

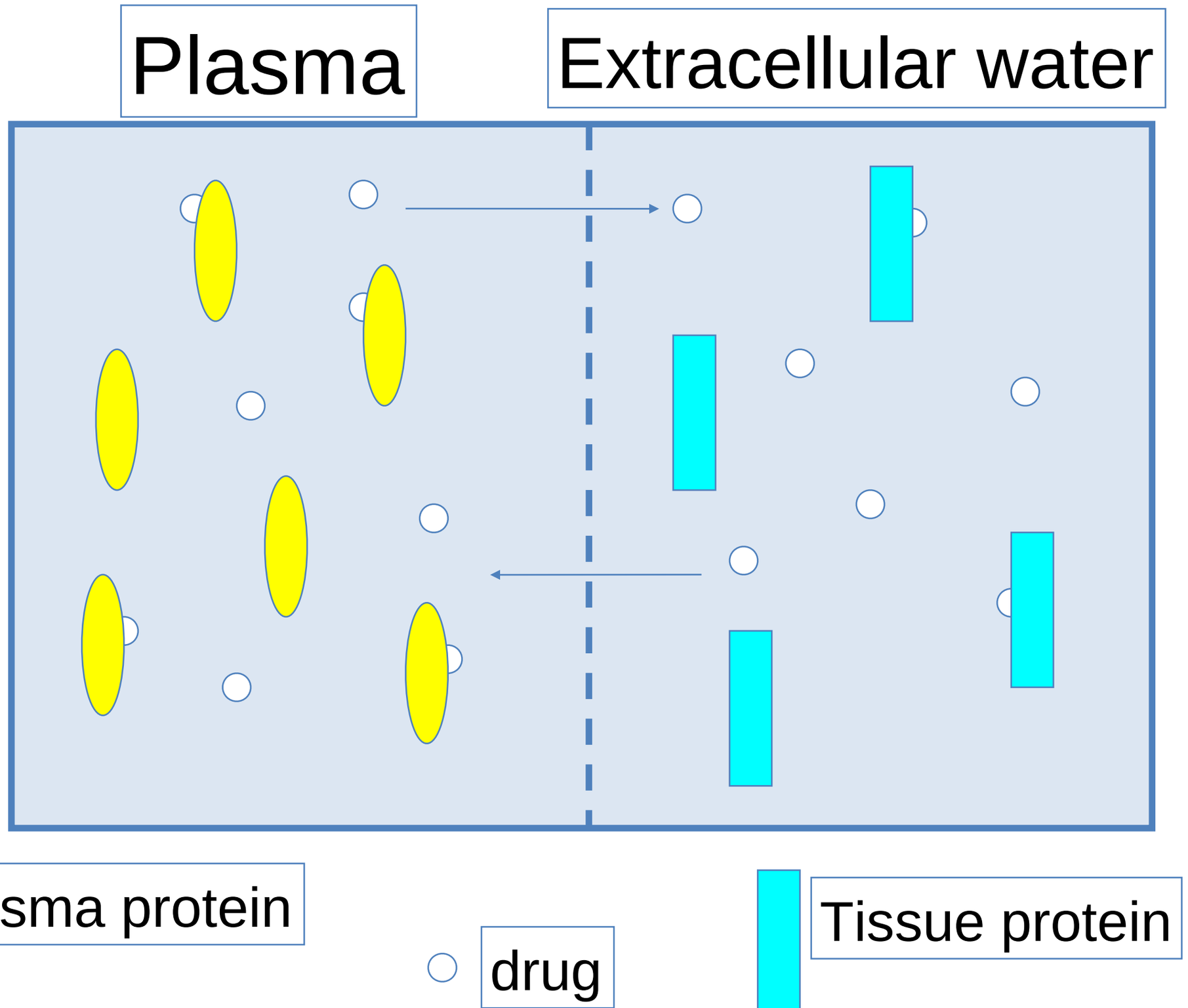
Protein-binding

- Only unbound drug is capable of crossing the placenta
- Drugs with low protein binding reach higher concentrations in the fetus than mom

Protein binding

- ✈ not only affects the activity of the drug (bound = inactive)
- ✈ But also can influence its distribution from one compartment to another.
- ✈ This is particularly true with respect to glomerular filtration and passive transport.

Free Drug + Protein $\overset{TM}{}$ Bound Drug


Plasma
Extracellular water
Plasma protein
drug
Tissue protein

Plasma Proteins

albumin

- primarily for acidic drugs

a_1-acid glycoprotein

- for basic drugs

Lipoproteins

- for some drugs

The fraction of total drug in plasma that is bound is determined by

- ✕ **the drug concentration,**
- ✕ **its affinity for the binding sites, and**
- ✕ **the number of binding sites.**

Distribution

- Depending on drug size and lipid solubility, drugs can distribute to body compartments.
- Brain, prostate, and eye tissues might be difficult to penetrate.

Distribution

The delivery of drug from the systemic circulation to tissues

(1) capillary permeability

(2) blood flow–tissue mass ratio (i.e., perfusion rate),

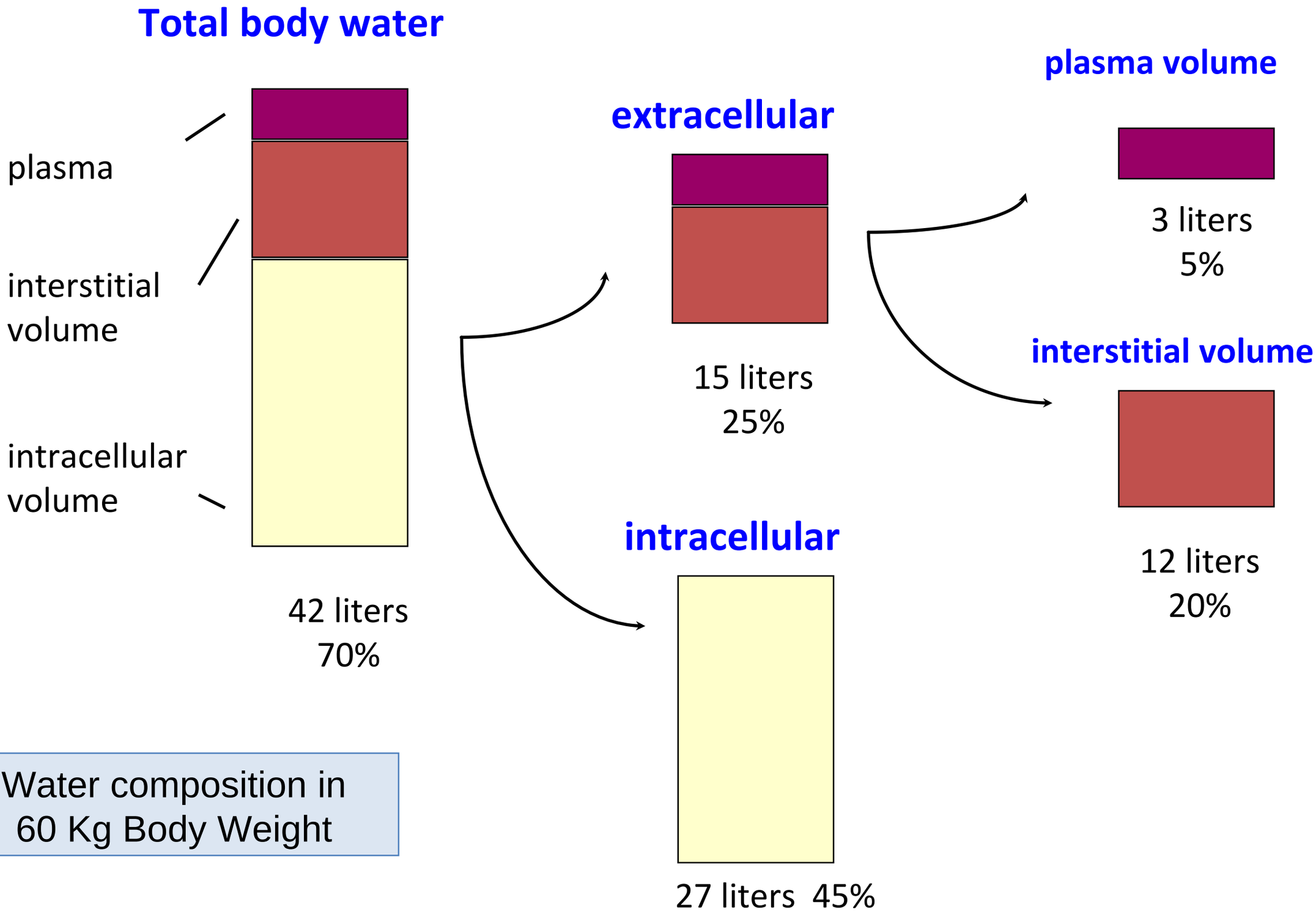
(3) extent of plasma protein and specific organ binding

(4) regional differences in pH,

(5) transport mechanisms available

(6) the permeability characteristics of specific tissue membranes.

Drug distribution and Body water



Water composition in
60 Kg Body Weight

Distribution

The total volume of the fluid compartments of the body into which drugs may be distributed is approximately **42 L** in a 60-kg adult.

These compartments include:

- Plasma water
- The interstitial fluid
- The intracellular fluid

A. Plasma:

Drug has very large molecular weight or bind extensively to the plasma proteins. So the drug is effectively trapped with the plasma (vascular) compartment.

In this case the drug will distribute in a volume that is about 6% of the body weight.

for example, in 60 kg individual, agents of this type, such as Heparin, will distribute in 3 L of body fluids.

Distribution

B. Extracellular: has low molecular weight but it is hydrophilic, it can move through the endothelial junctions but cannot cross the membrane to inter the cells.

So drugs like aminoglycosides, will distribute into a volume equal the sum of the plasma water and the interstitial fluids.

C. Total body water: has low molecular weight and hydrophobic, here the drug move through the membranes into the cells. Here the drug will distribute into a volume of about 60% of the body weight.

note: Some drugs, lipid soluble ones, stored in the fatty tissue in an equilibrium with free circulating drug

Distribution

- Some areas of the body are not accessible to drugs due to anatomic barriers,

- The capillary membrane between the plasma and brain cells is much less permeable than is the membrane between plasma and another tissue.

- Therefore the transfer of drugs into the brain is regulated by what is called “blood brain barrier”

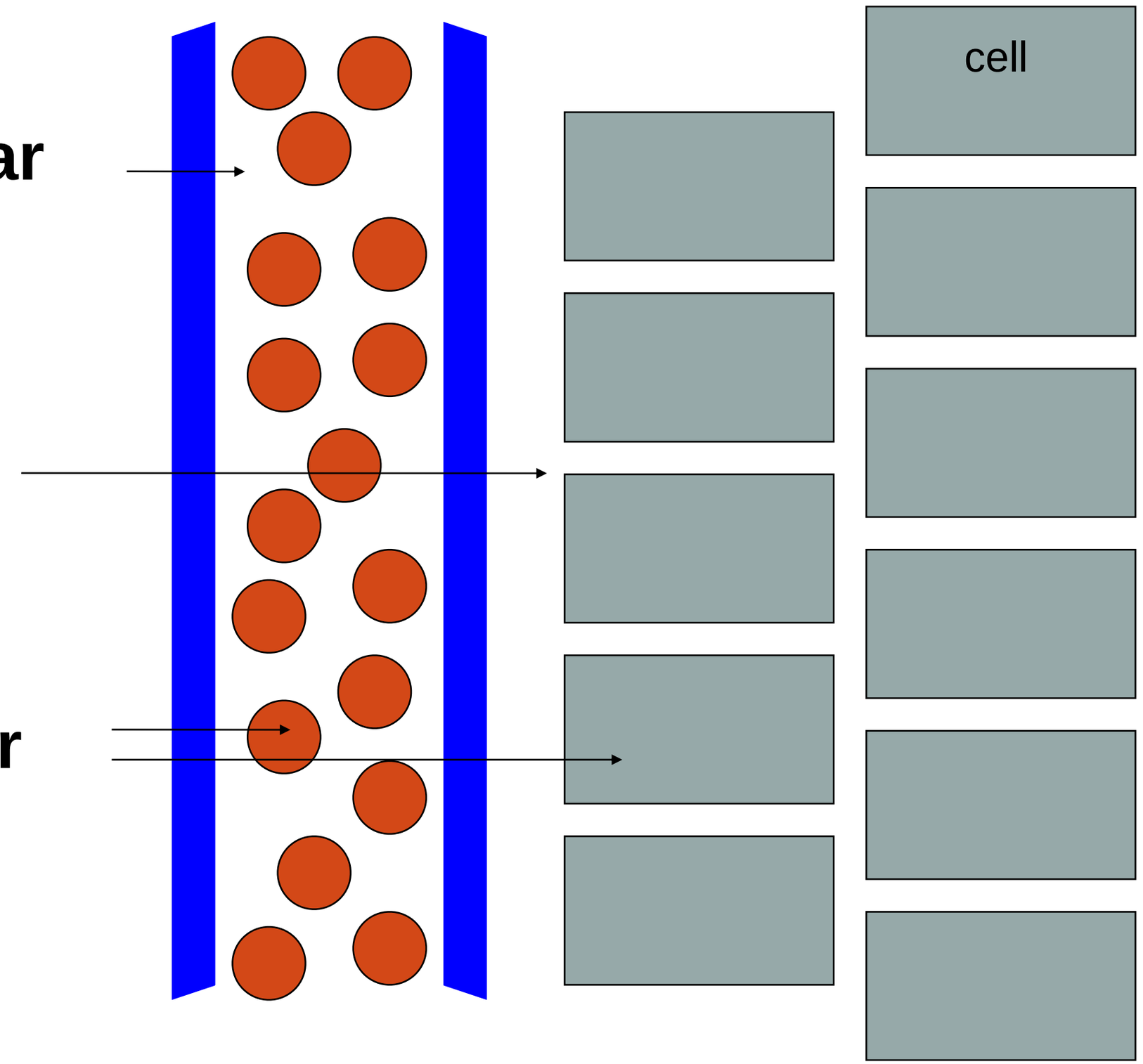
  1. it is only permeable to lipophilic agents
  2. impermeable to ionic hydrophilic agents
  3. Amino acids, glucose etc have specific uptake systems

Drug distribution and Body water

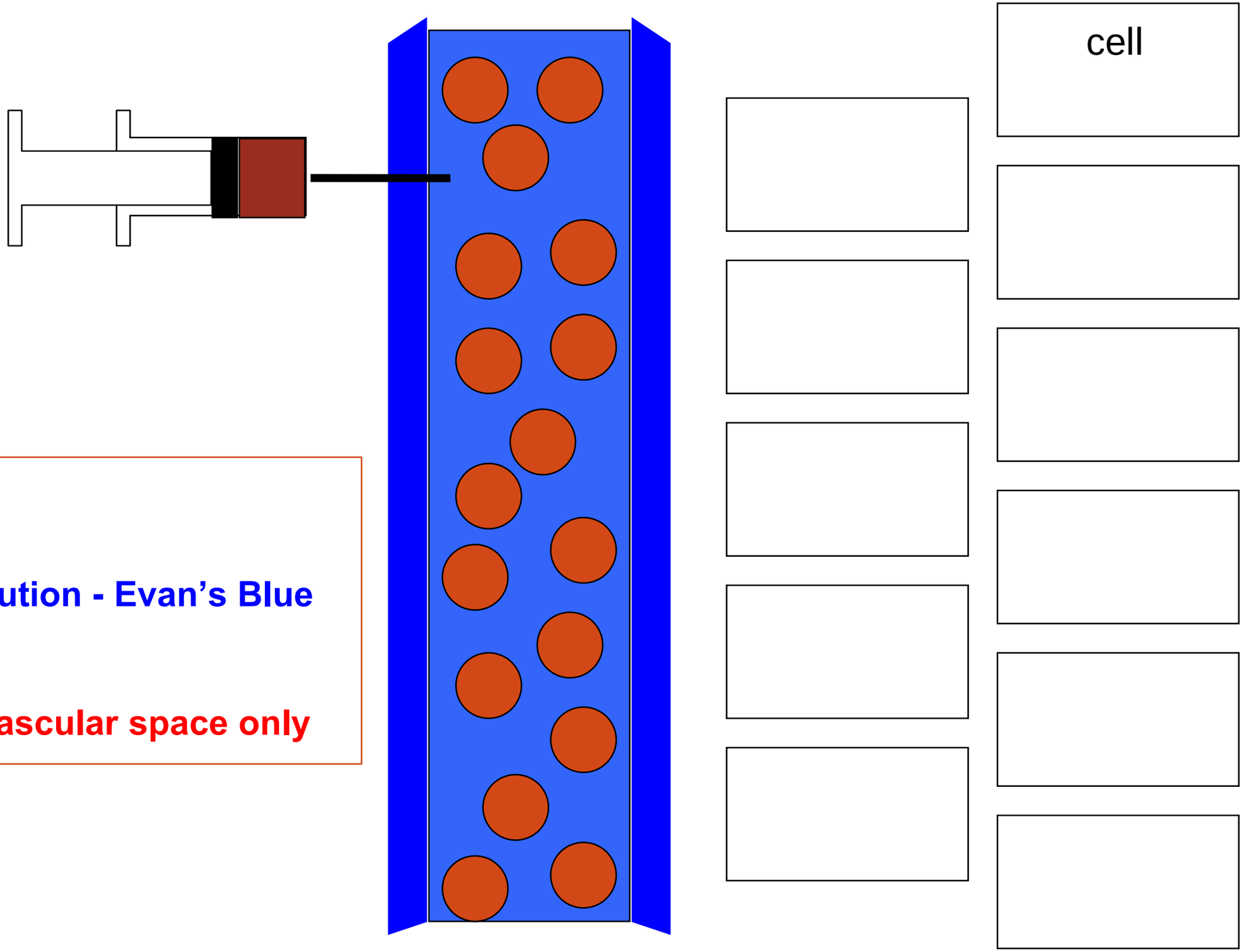
Intra-vascular

Interstitial

Intra-cellular



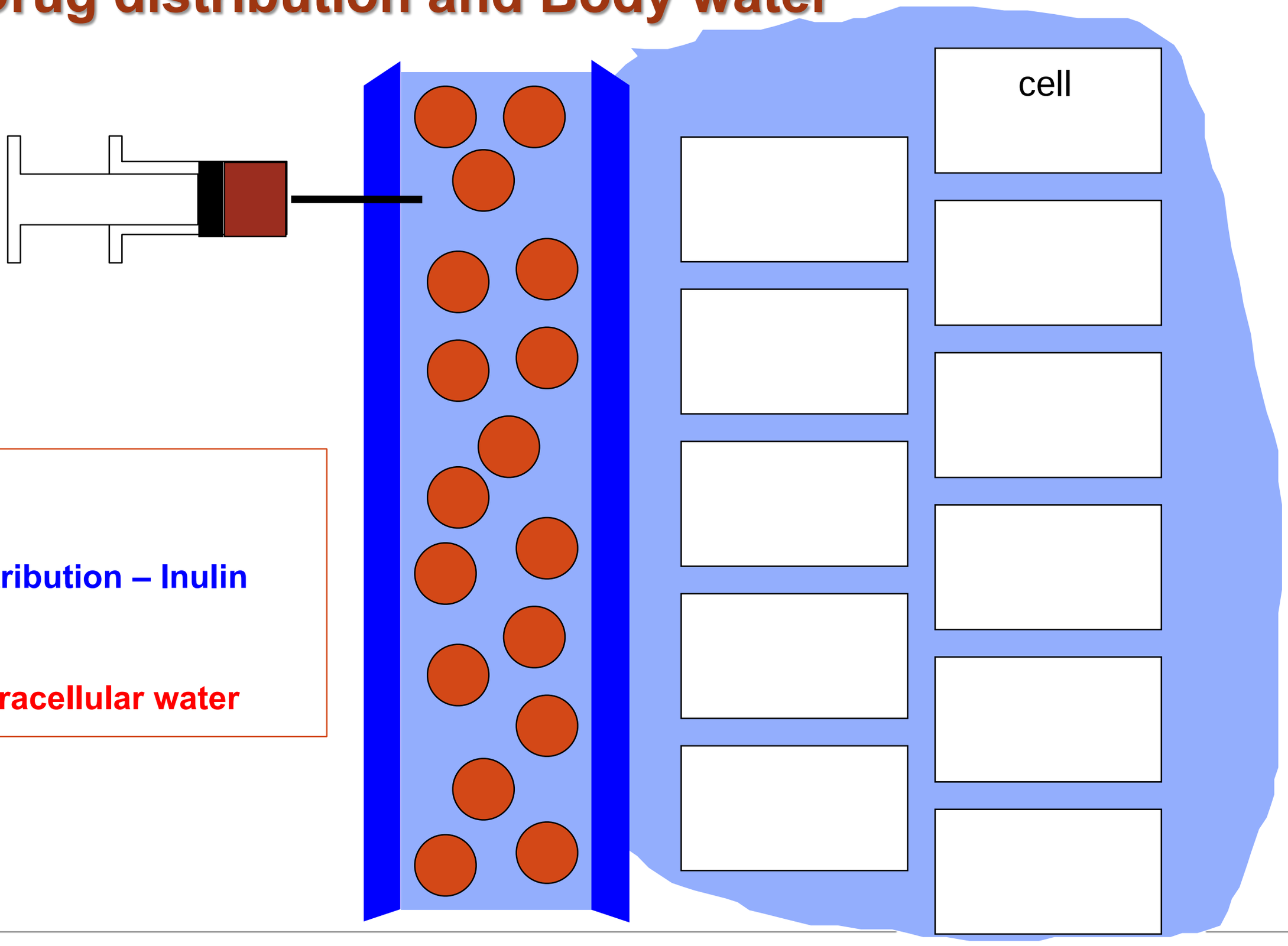
Drug distribution and Body water



Distribution - Evan’s Blue

Intra-vascular space only

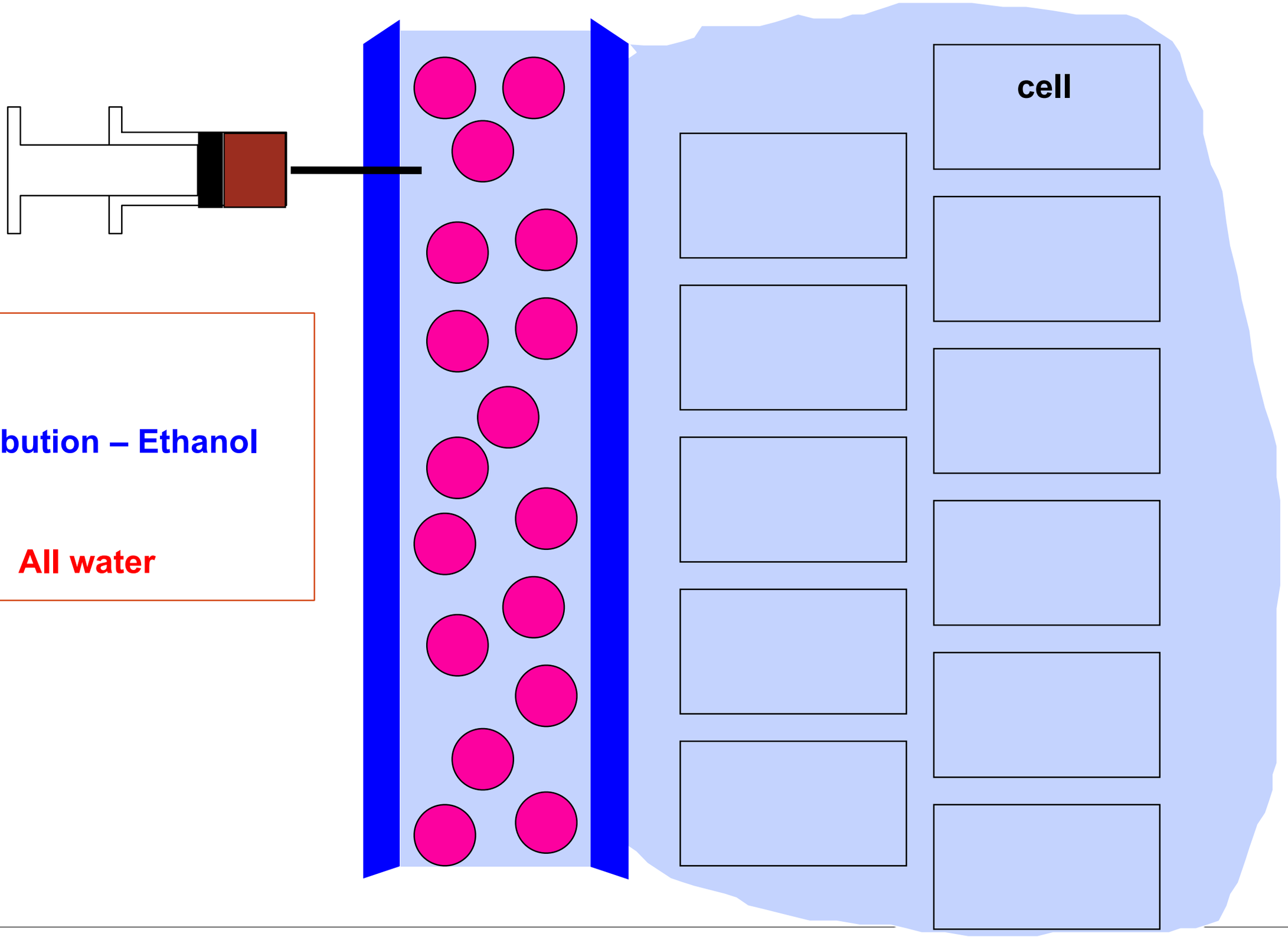
Drug distribution and Body water



Distribution – Inulin

Extracellular water

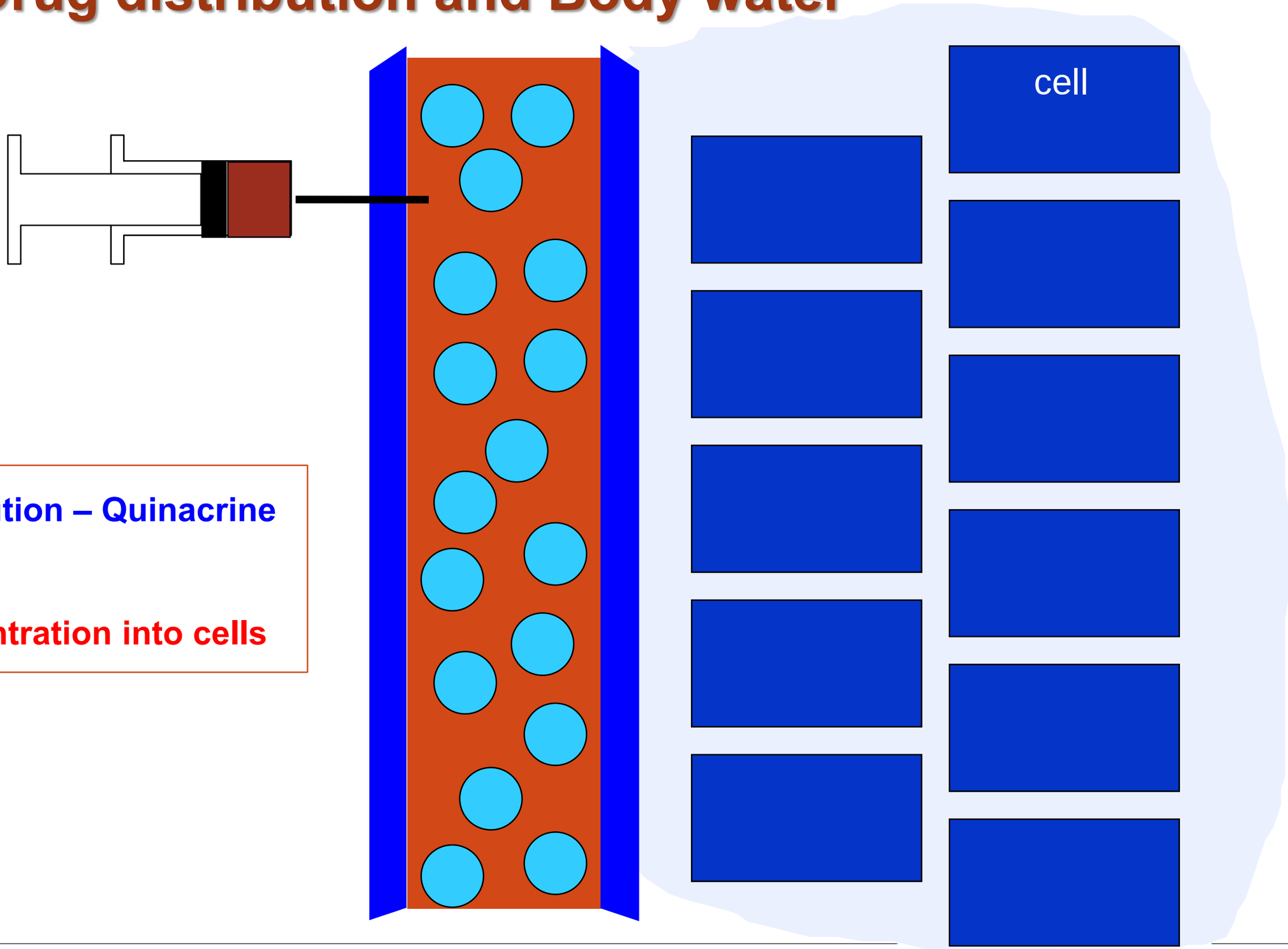
Drug distribution and Body water



Distribution – Ethanol

All water

Drug distribution and Body water

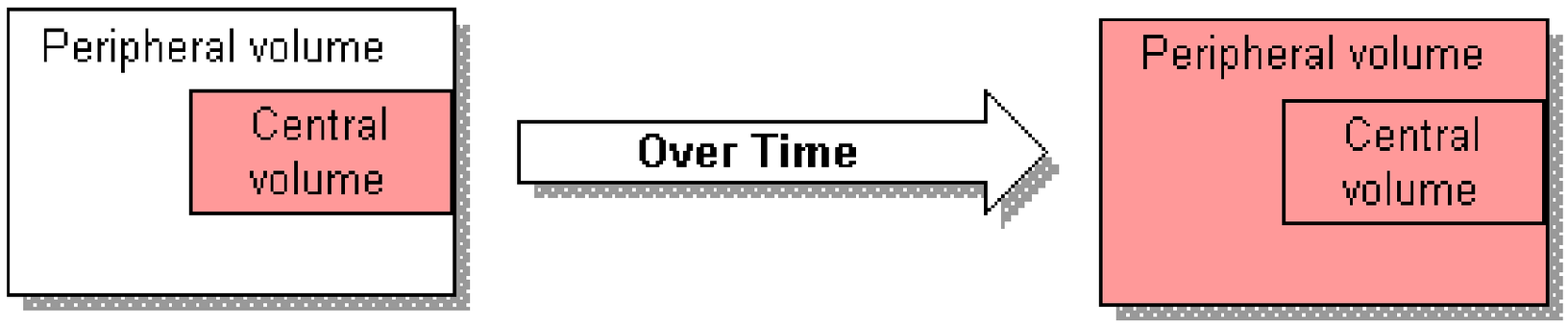


Distribution – Quinacrine

Concentration into cells

Volume of Distribution (Vd)

- A measure of the tendency of a drug to move out of the blood plasma to some other site.
- Or A measure of extend of distribution



Volume of Distribution (Vd)

How can we measure the extent of distribution?

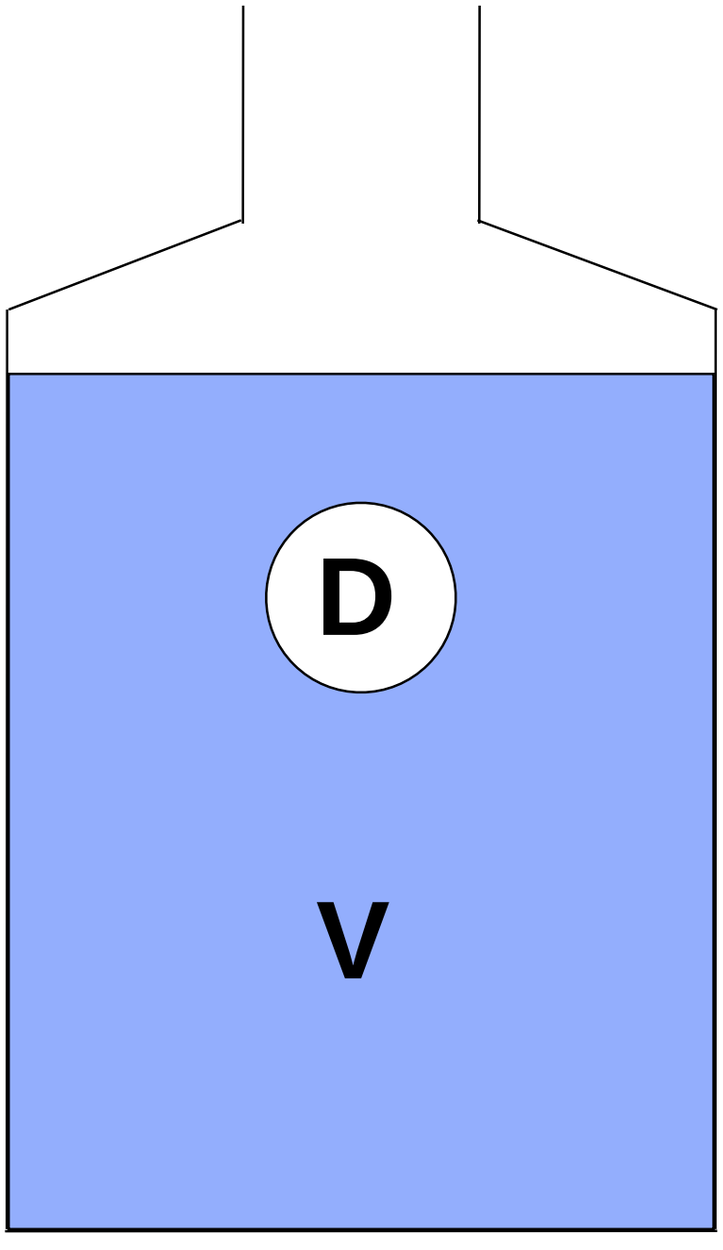
Apparent volume of distribution (V_d)

$$V_d = \frac{\text{amount of drug in body}}{\text{plasma drug concentration}}$$

VOLUME OF DISTRIBUTION FOR SOME DRUGS

DRUG	Vd (L)
cocaine	140
clonazepam	210
amitriptyline	1050
amiodarone	~5000

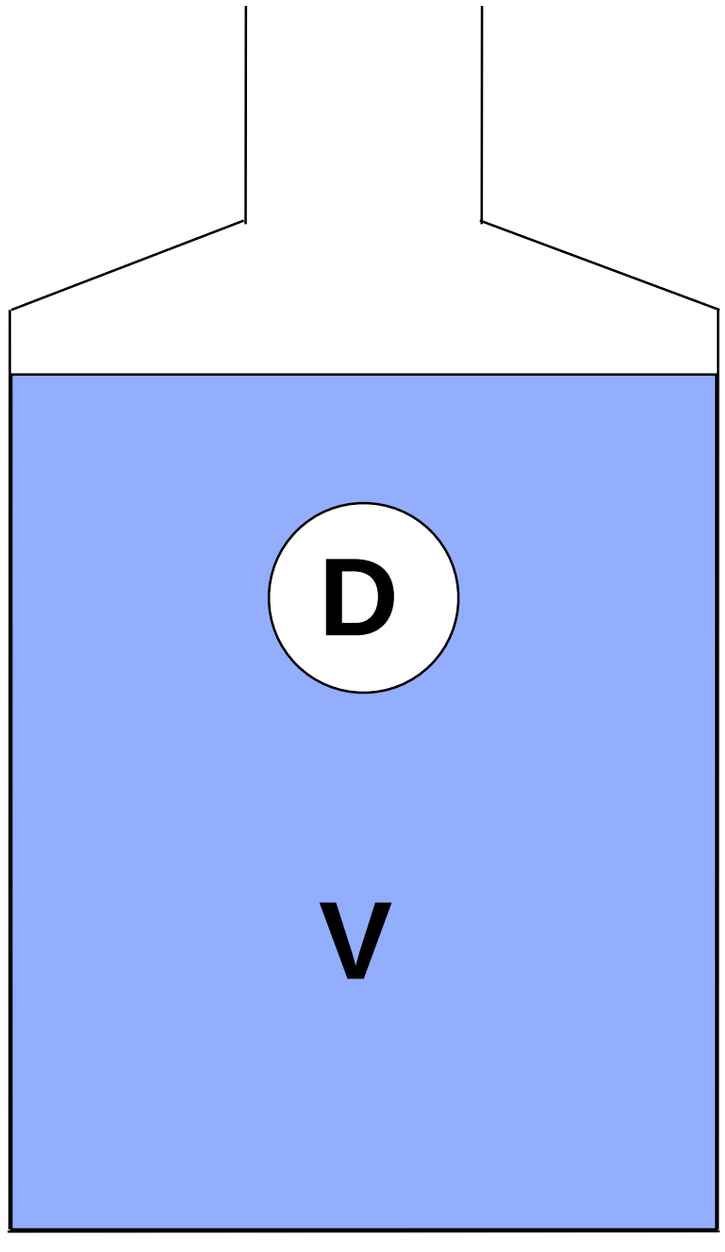
Volume of distribution



$$C = D/V$$

$$V = D/C$$

Volume of distribution - an example



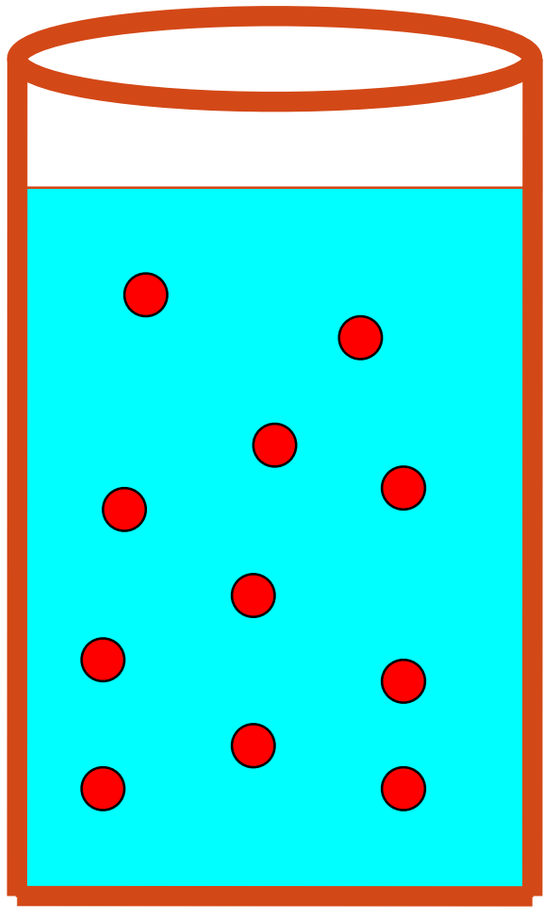
D = 50 mg

C = 2.5 mg/L

V = D/C

= 50mg / 2.5mg/L

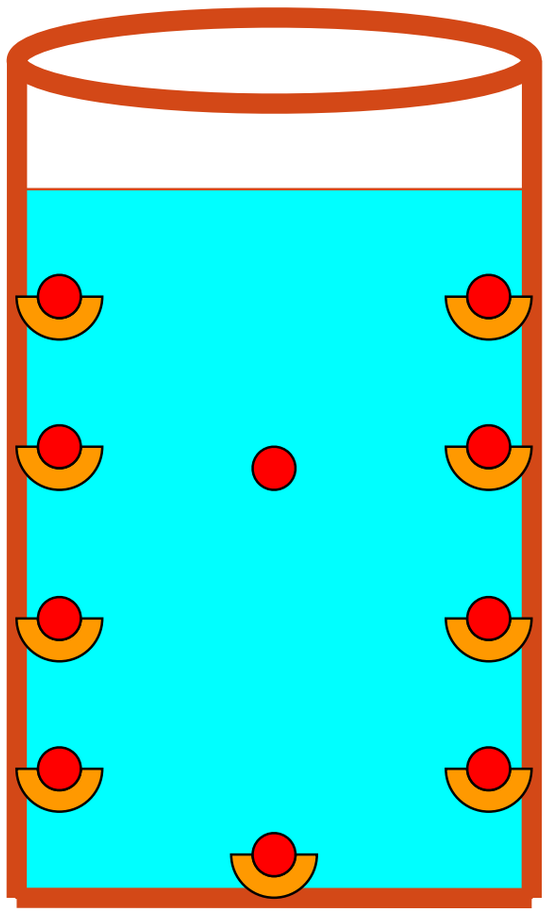
= 20 Litres



What is the volume of water in the beaker?

$$\text{Volume} = \frac{\text{amount}}{\text{concentration}}$$

$$\text{Volume} = \frac{10\ \text{mg}}{10\ \text{mg/L}} = 1L$$



What is the volume of water in the beaker?

$$\text{Volume} = \frac{\text{amount}}{\text{concentration}}$$

$$\text{Volume} = \frac{10mg}{1mg/L} = 10L$$

Volumes of distribution (Vd)

(In litres for average 70 Kg adult human)

Warfarin	7
Gentamicin	16
Theophylline	35
Cimetidine	140
Digoxin	510
Mianserin	910
Quinacrine	50,000

Small vol. Mainly stays in plasma little in tissues.

Medium vol. Similar concs in plasma and tissues

Large vol. Mainly in tissues, little in plasma.

Volume of distribution and body weight

Vd depends upon body size.

May be quoted as L/kg (Litres per kg body weight)

e.g. Theophylline Vd = 0.48 L/kg

For 60 kg adult, Vd = 0.48 L/kg x 60 kg

= 28.8 L

Practice calculation

A dose of analgesic (50mg) is administered i.v. and a blood sample is taken shortly afterwards. The initial concentration of analgesic in the blood sample is 0.85 $\mu g.ml^{-1}$.

Calculate the volume of distribution of the analgesic (in Litres).

Model solution

Mixed units!

$V = D/C_0$

$= 50\ mg\ /\ 0.85\ \mu g.ml^{-1}$

$= 50{,}000\ \mu g\ /\ 0.85\ \mu g.ml^{-1}$

$= 58{,}824\ ml$

$= 59\ Litres$

Metabolism

- **Drugs can be broken down(metabolized) in the body by various mechanisms.**
- **Metabolism usually results in compounds which can be excreted.**
- **Metabolism can:**
  - **Inactivate the drug**
  - **Activate the drug**
  - **Produce other active metabolites.**

Metabolism

- **Liver is the major site for drug metabolism.**
- **Also, the kidneys, the g.i.t, plasma, and lungs can metabolize drugs.**
- **Metabolism can be affected by:**
  - **Disease state.**
  - **Blood flow.**
  - **Inducers and Inhibitors.**
  - **Genetic background of the patient.**
  - **Tolerance.**

Metabolism

- The liver is the major side of metabolism for many drugs, but other organs, such as lungs and kidney can also metabolize drugs.

- Many lipid soluble drugs are not readily eliminated from the body and must be conjugated or metabolized to compounds that are more polar and less lipid soluble before being excreted.

- Metabolism often, but not always, results in inactivation of the compounds.

- Some drugs are activated by metabolism, these substances called prodrugs.

Phase I metabolism

- Drug metabolism occur in two phases:

- Phase I reactions function (e.g., oxidation, reduction, hydrolysis) alter chemical reactivity and increase water solubility.

- Phase I reaction frequently catalysis by the cytochrome P450 system (also called microsomal mixed function oxidase).

$$\mathbf{Drug + O_2 + NADPH + H^+ \rightarrow Drug_{modified} + H_2O + NADP^+}$$

- To date, 12 unique isoforms of this enzymatic system (CYP 2D6, CYP3A4) have been identified to play a role in human drug metabolism.

Phase II metabolism

- If the metabolite from phase I is polar enough it will excreted by the kidney, But if it is still lipophilic to be retained in the kidney, a subequence Phase II metabolism will take place.

- Phase II consist of conjugation reaction with endogenous substances, such as, glucuronic acid, sulfuric acid, or an amino acid.

- Results in polar and usually more water soluble compounds.

Cytochrome P450 system

- Cytochrome P450 system dependant enzymes are important target for drug interaction because they can be induced or inhibited by certain drugs.

- Cytochrome enzymes Inducers like Rifampin and Carbamazepine are capable of increasing the synthesis of one or more of isoforms. For example, Rifampin significantly decreases the plasma concentration of HIV protease inhibitors.

- Cytochrome enzymes inhibitors, Omeprazole inhibits three CYP isoforms that are responsible for Warfarin metabolism, leading in an elevation in the Warfarin concentration, and so greater inhibition of coagulation, leading in to more risk of serious bleeding reaction.

Elimination

- It is a process in which drugs are transferred from the internal to the external environment.

- Occur via a number of routes , the most important being through the kidney into the urine.

- Other routes include the bile, intestine, lung, or milk in nursing mother.

- Drugs eliminated through these routes tend to be lipid soluble and unionized.

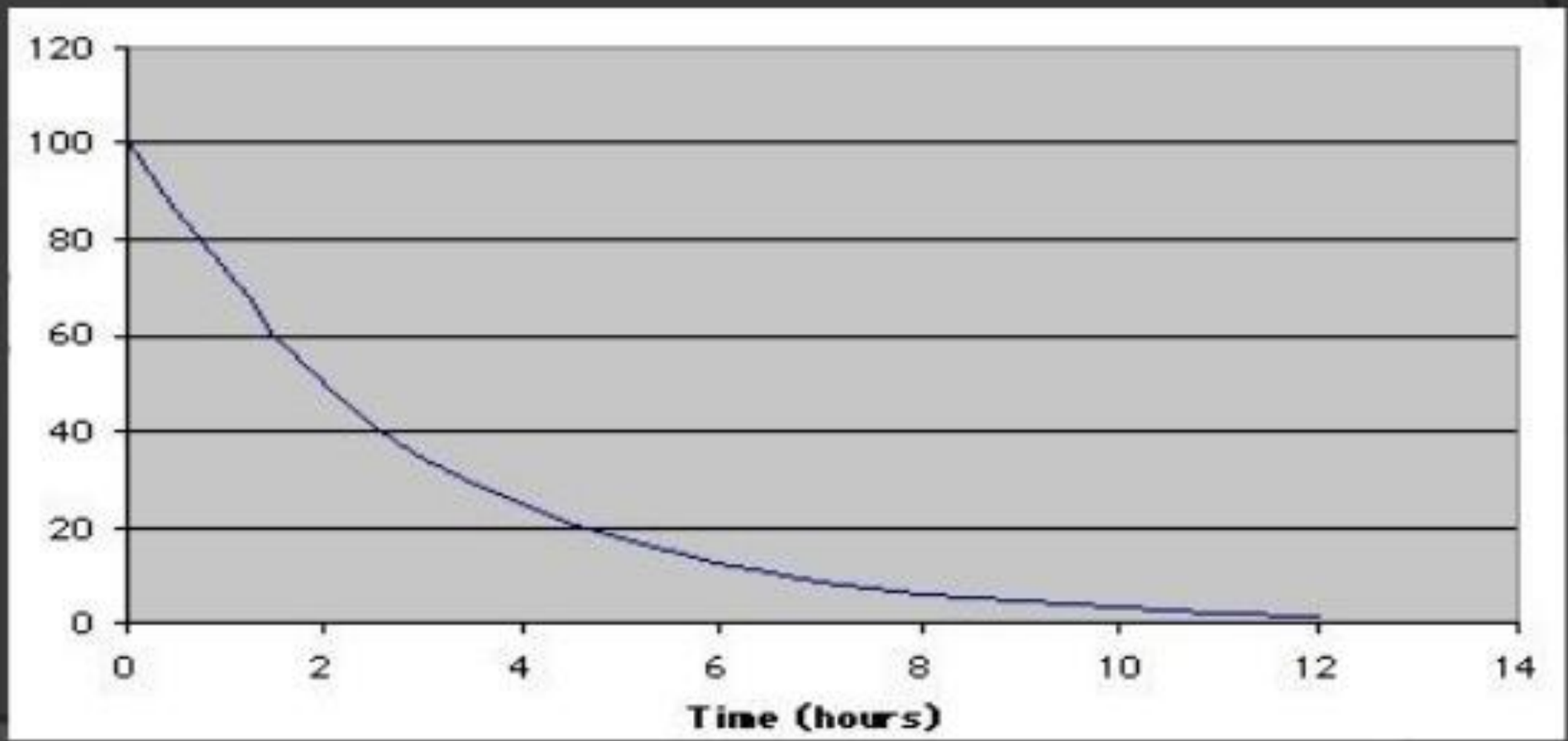
Elimination

- Drugs can be eliminated through various routes (kidney, lungs, sweat, feces).
- Metabolism usually results in inactive metabolites which are also water soluble and therefore excretable by the kidneys.
- Weak acids are excreted faster in alkaline urine.
- Weak bases are excreted faster in acidic urine.
- Elimination follows first-order kinetics of decay.

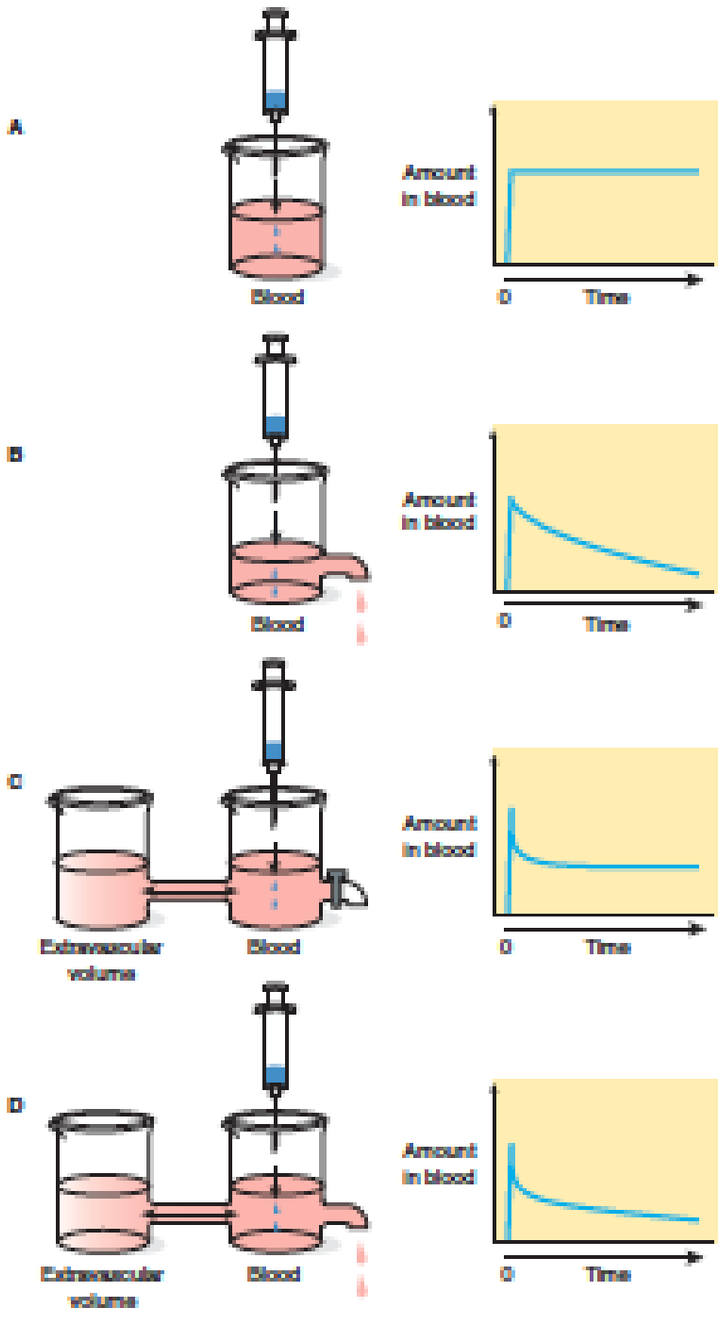
Plasma half life ($t_{1/2}$) of drug

$$t_{1/2} = \frac{0.7 \times V}{CL}$$

- Time to decline conc. from 100 to 50 = 2 hr
- So, $t_{1/2}$ of this drug is 2 hr

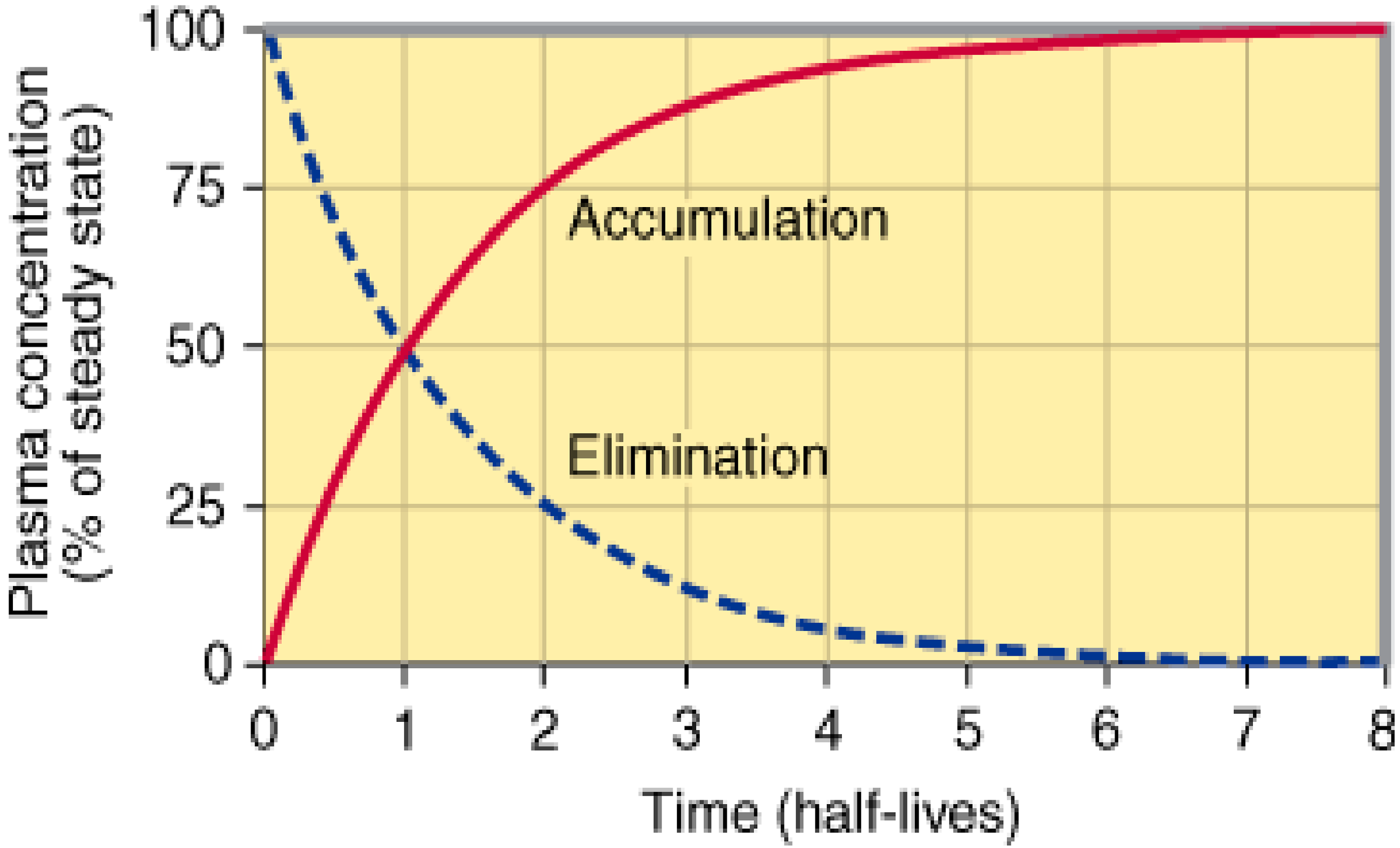


Clearance: pharmacokinetic measurement of the volume of plasma from which a substance is completely removed per unit time; the usual units are mL/min. The quantity reflects the rate of drug elimination divided by plasma concentration.



$$CL = \frac{\text{Rate of elimination}}{C}$$

Time course of drug accumulation and elimination after oral and IV administration.



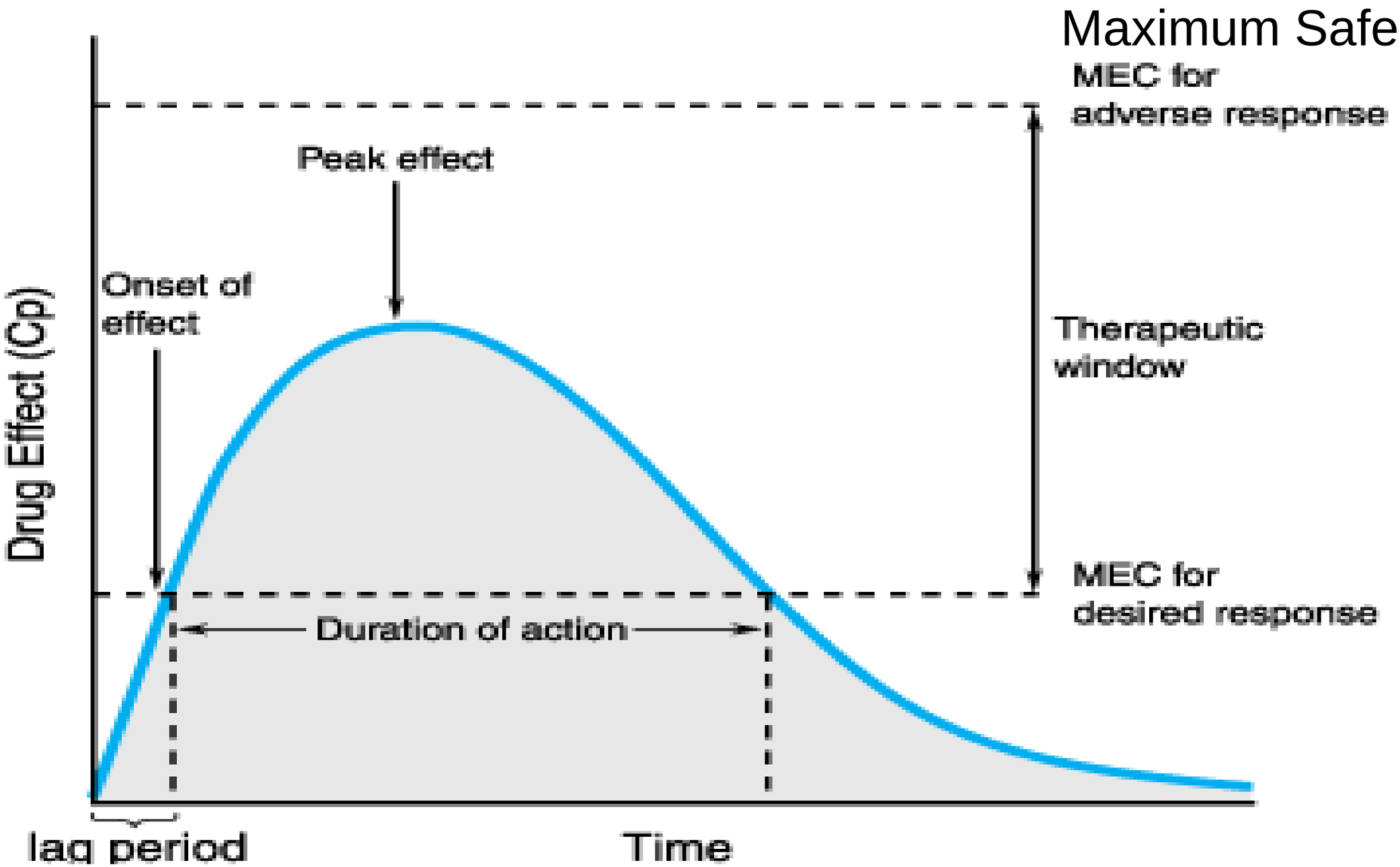
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

The time course of drug accumulation and elimination.
Solid line: Plasma concentrations reflecting drug accumulation during a constant-rate infusion of a drug. Fifty percent of the steady-state concentration is reached after one half-life, 75% after two half-lives, and over 90% after four half-lives.
Dashed line:b Plasma concentrations reflecting drug elimination after a constant rate infusion of a drug had reached steady state. Fifty percent of the drug is lost after one half-life, 75% after two half-lives, etc.
The “**rule of thumb”** that four half-lives must elapse after starting a drug-dosing regimen before full effects will be seen is based on the approach of the accumulation curve to over 90% of the final steady-state concentration.

Dosage Regimens

- **Single administration.**
- **Frequent administration.**
  - **Loading dose.**
  - **Maintenance dose.**

Drug concentration/effect and relationship to the therapeutic window after single oral dose

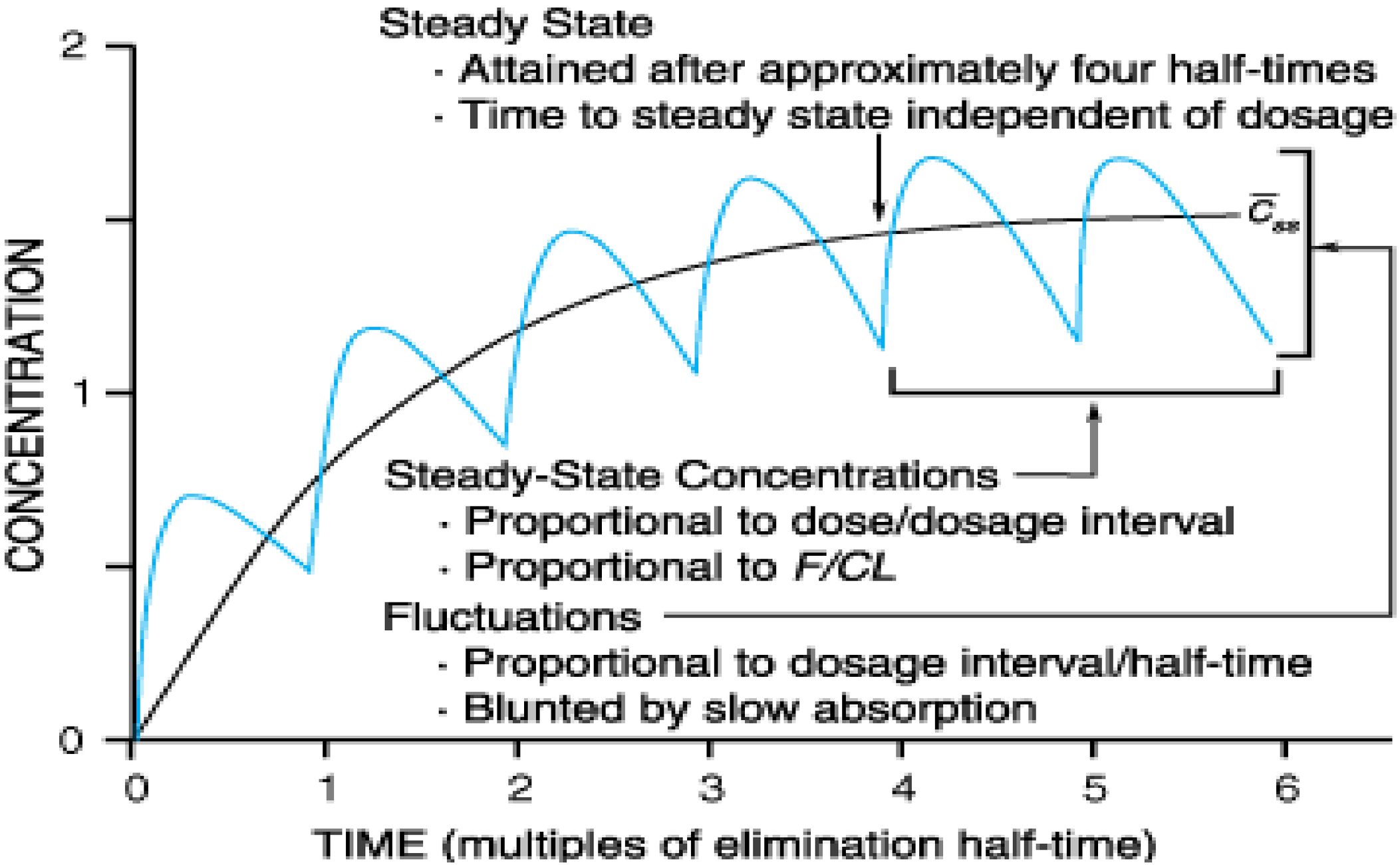


Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com

Drug concentration/effect and relationship to the therapeutic window after single oral dose

- **A lag period is present before the plasma drug concentration exceeds the minimum effective concentration (MEC) for the desired effect.**
- **Following onset of the response, the intensity of the effect increases as the drug continues to be absorbed and distributed.**
- **This reaches a peak, after which drug elimination results in a decline in concentration and in intensity.**
- **Effect disappears when the drug concentration falls below the MEC. Accordingly, the duration of a drug's action is determined by the time period over which concentrations exceed the MEC.**
- **An MEC exists for each adverse response, and if drug concentration exceeds this, toxicity will result.**
- **The therapeutic goal is to obtain and maintain concentrations within the therapeutic window for the desired response with a minimum of toxicity.**
- **Drug response below the MEC for the desired effect will be subtherapeutic.**

Pattern of drug accumulation during repeated administration of a drug at intervals equal to its elimination half-time



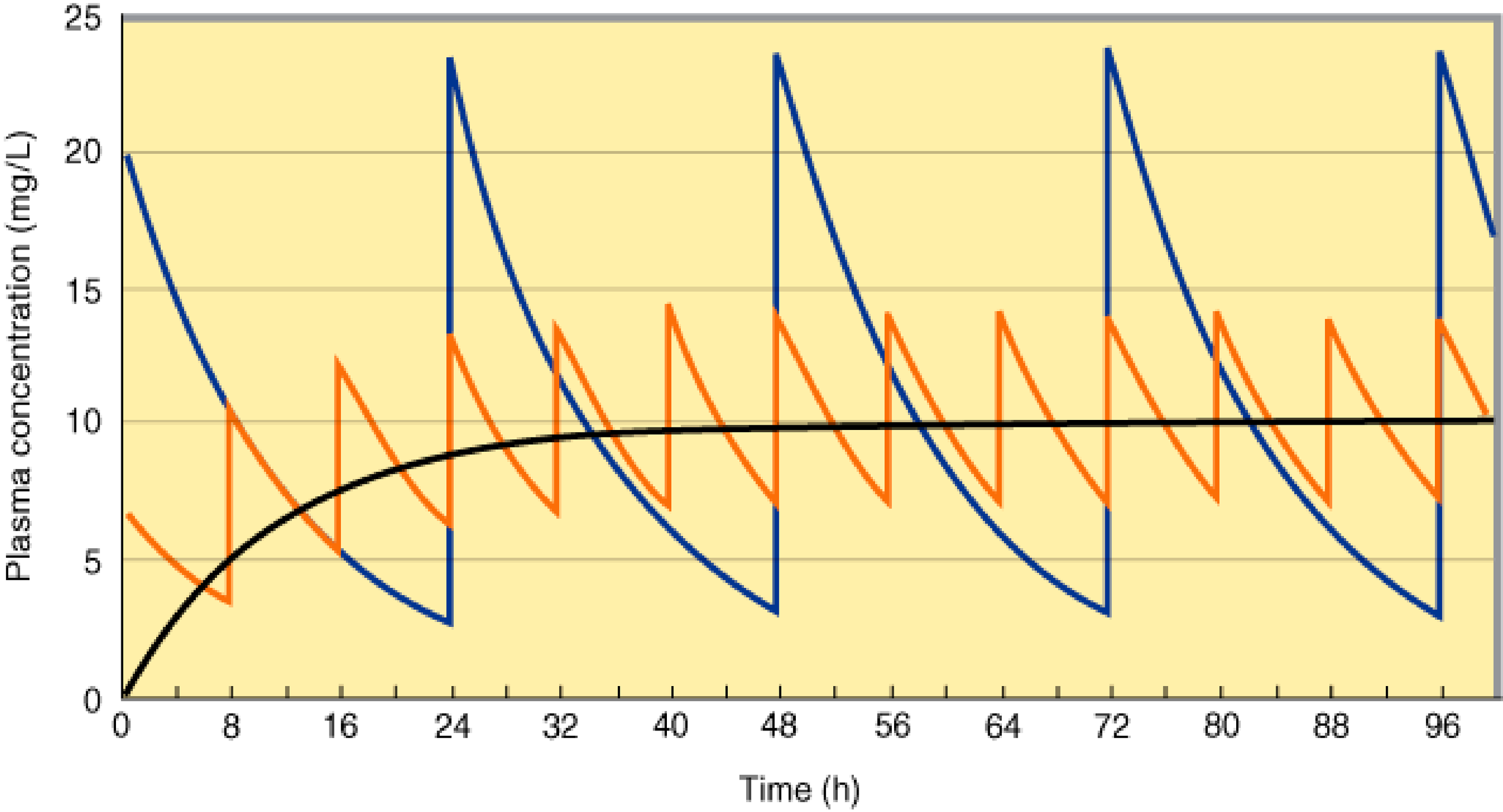
Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com

Time course of drug accumulation and elimination

- During a constant rate infusion of a drug, fifty percent of the steady-state concentration is reached after one half-life, 75% after two half-lives, and over 90% after four half-lives.
- After stopping a constant rate infusion of a drug had reached steady state, fifty percent of the drug is lost after one half-life, 75% after two half-lives,…. etc.
- The rule that four half lives must elapse after starting a drug-dosing regimen before full effects will be seen, is based on the approach of the accumulation curve to over 90% of the final steady-state concentration.

Relationship between frequency of dosing and maximum and minimum plasma concentrations

when a steady-state plasma level is desired



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

Sources of Variability in Therapeutic Responses

Similar drugs usually produce similar qualities of responses in patients, but might produce different intensities and duration of effects.

- **Dose, Dosage schedule, and Route of administration.**
- **Diurnal variation ”Chronopharmacology”.**
- **Age and sex of the patient.**
- **Drug reactions.**
- **Drug interactions: other drugs, diet, and environment.**
- **Placebo effect.**
- **Intercurrent illnesses.**
- **Tolerance.**
- **Genetic or racial factors, “Pharmacogenetics”.**