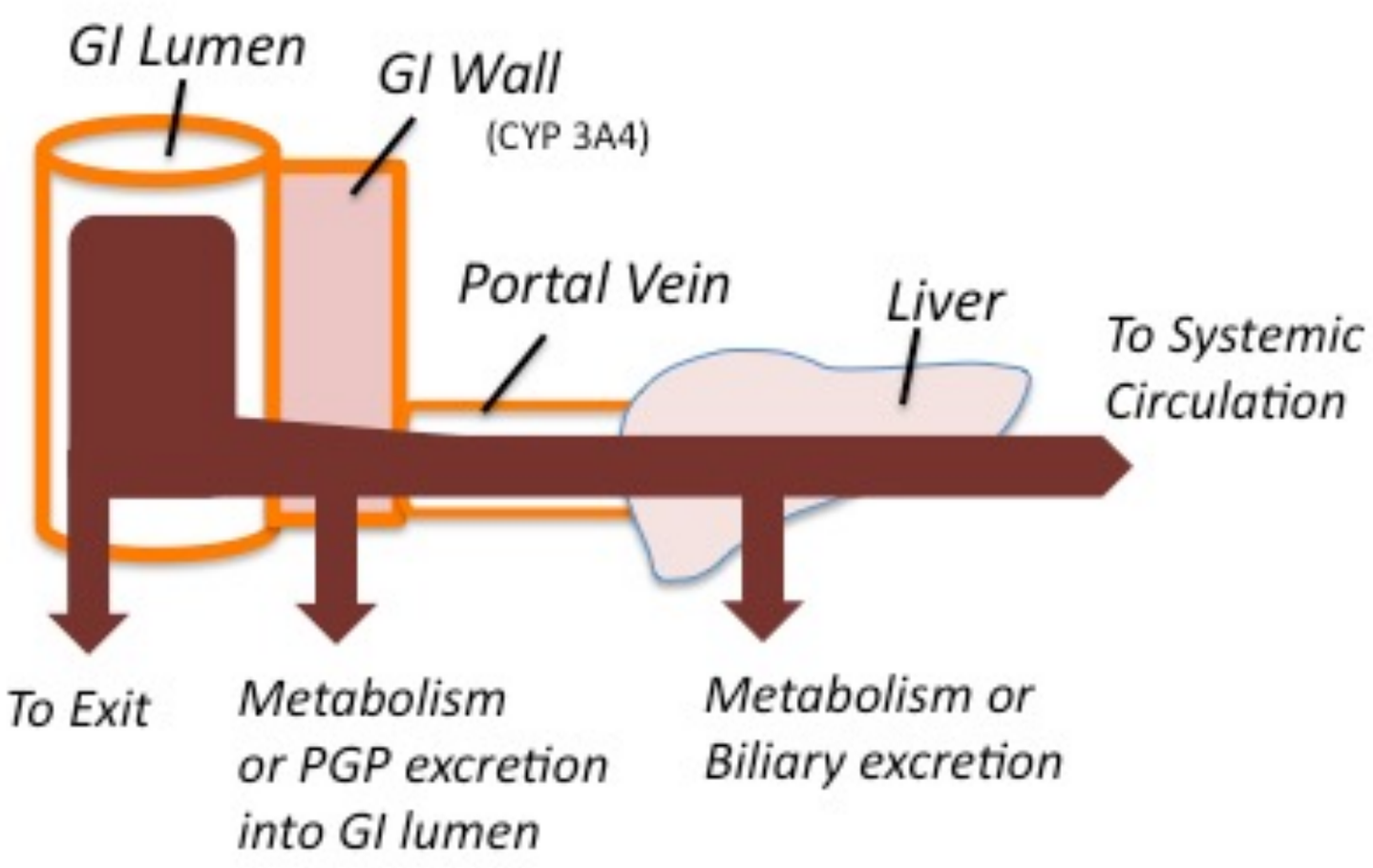
Pharmacokinetic parameters

- apparent volume of distribution V_d
- clearance Cl
- bioavailability F
- elimination half-life $t_{1/2}$

Bioavailability (F)

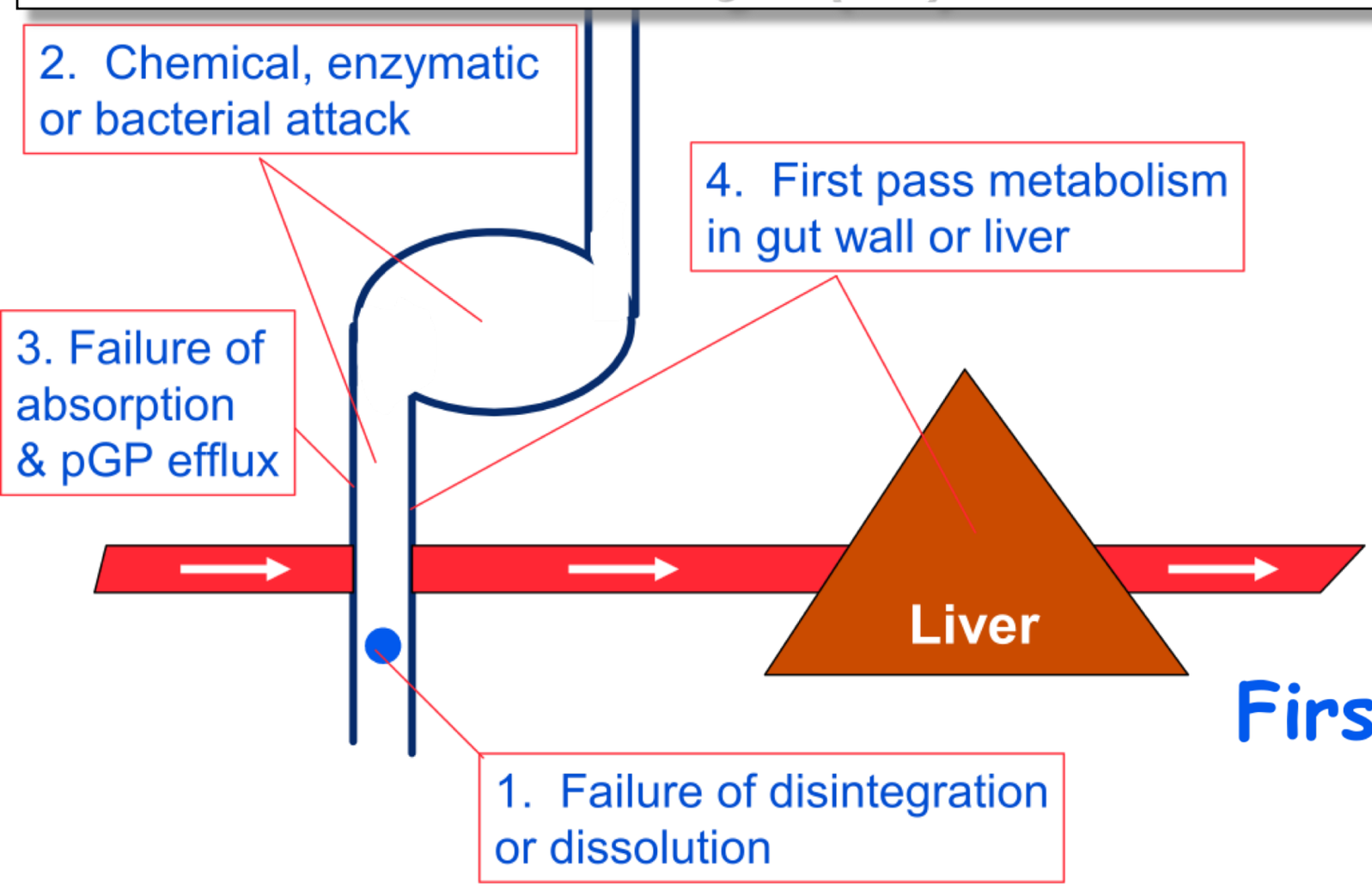
It is the percentage (or fraction) of a drug that reaches the systemic circulation in a chemically unaltered form and becomes available for the pharmacological effect after oral administration

After intravascular administration, bioavailability is 100%



F = Fractional bioavailability (has no units)

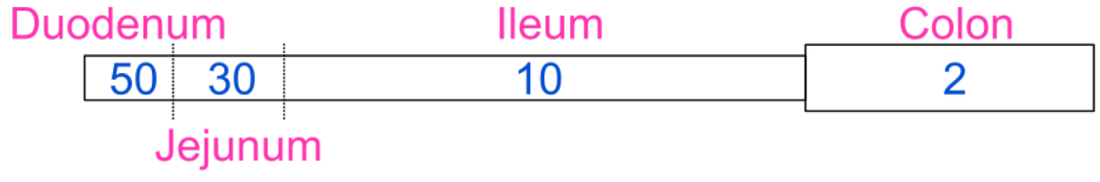
Bioavailability (F)



First pass metabolism in the gut wall

Intestinal epithelium is rich in drug metabolising enzymes. Main Cyt P450 is CYP3A4

Cytochrome P450 activity in intestinal epithelium relative to liver (%)

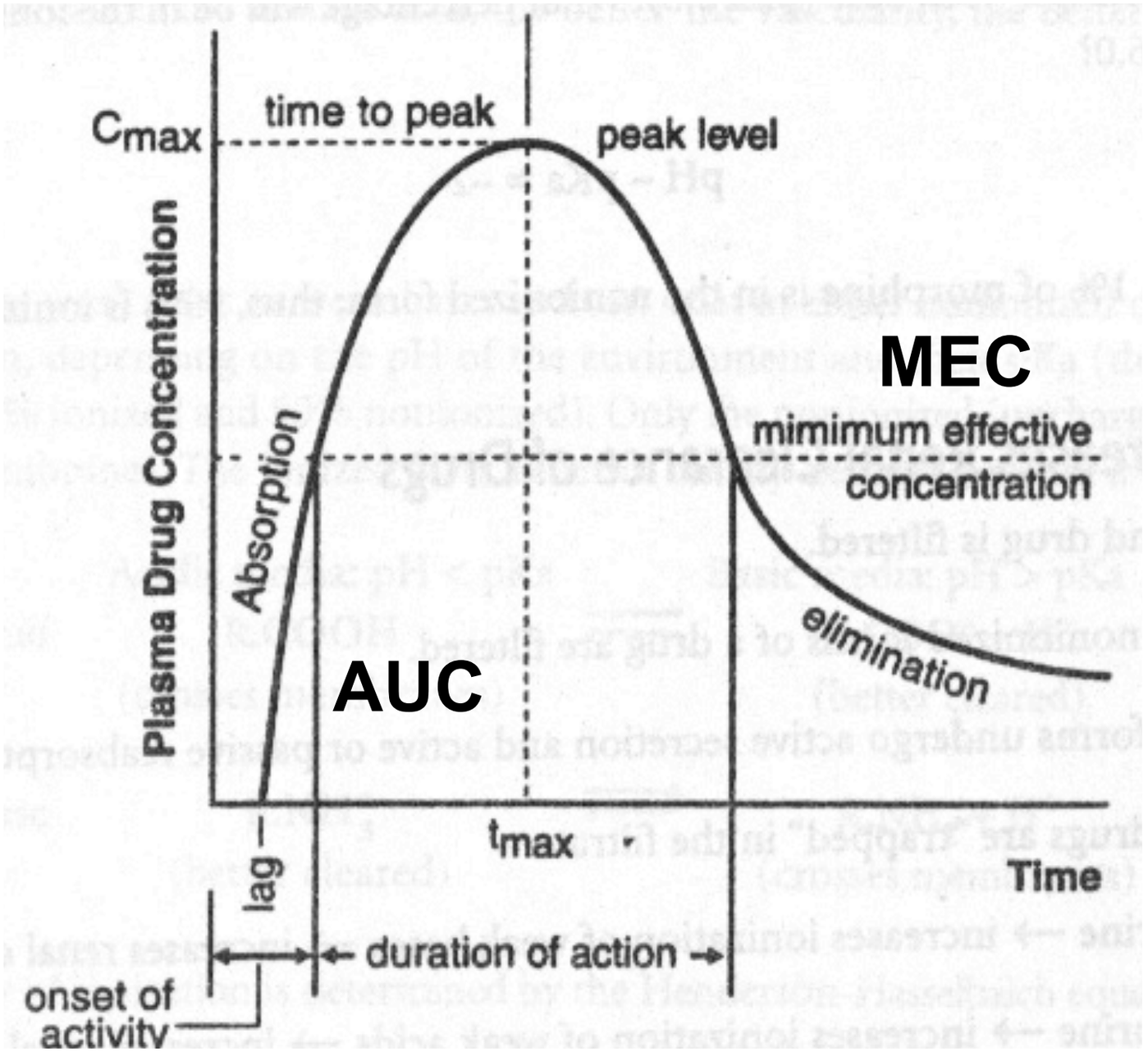


Drug Plasma level curve after oral administration

C_{max} = maximal drug concentration obtained with the dose

t_{max} = time at which C_{max} occurs

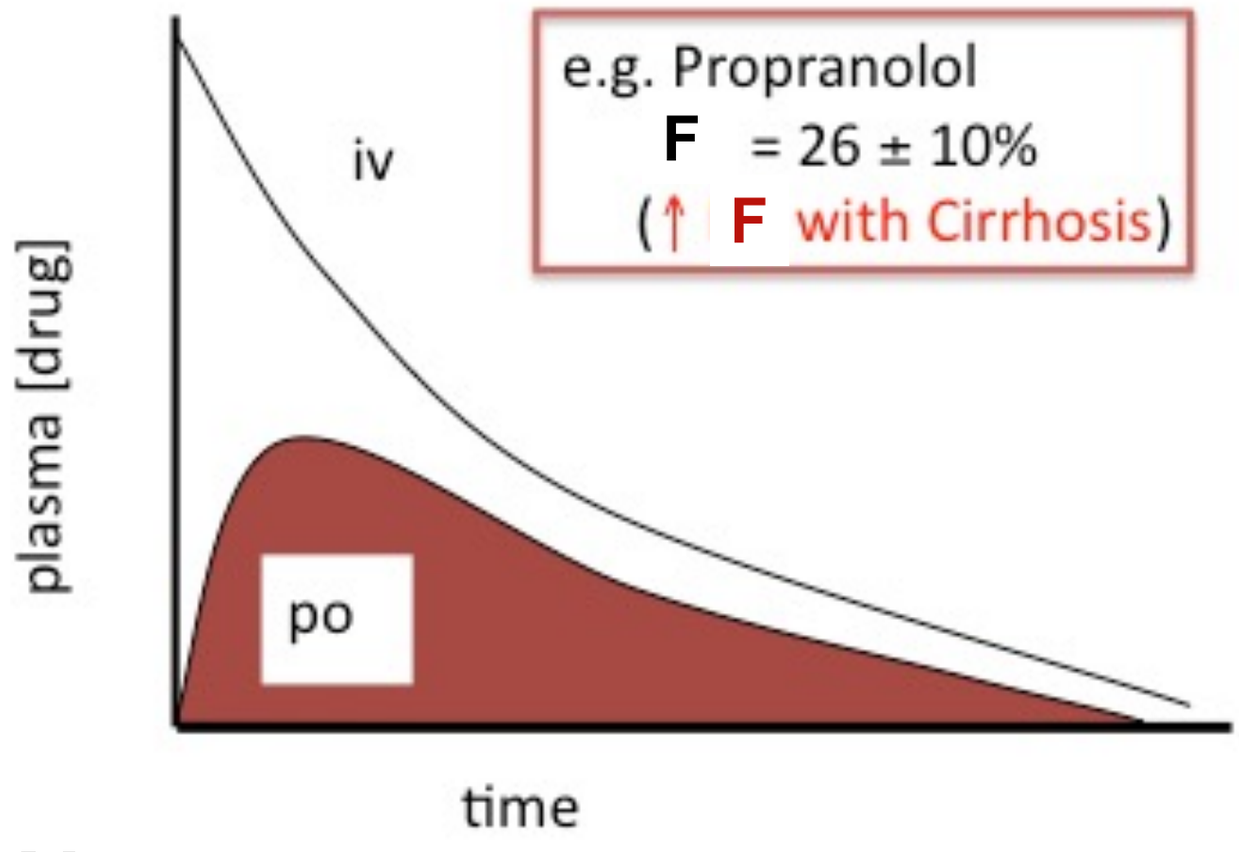
AUC = Area Under the Curve



Bioavailability (F)

F is calculated by comparison of the area under the plasma concentration time curve (AUC) after I.V. administration of a drug with that observed when the same drug is given at the same dose by another route e.g. oral

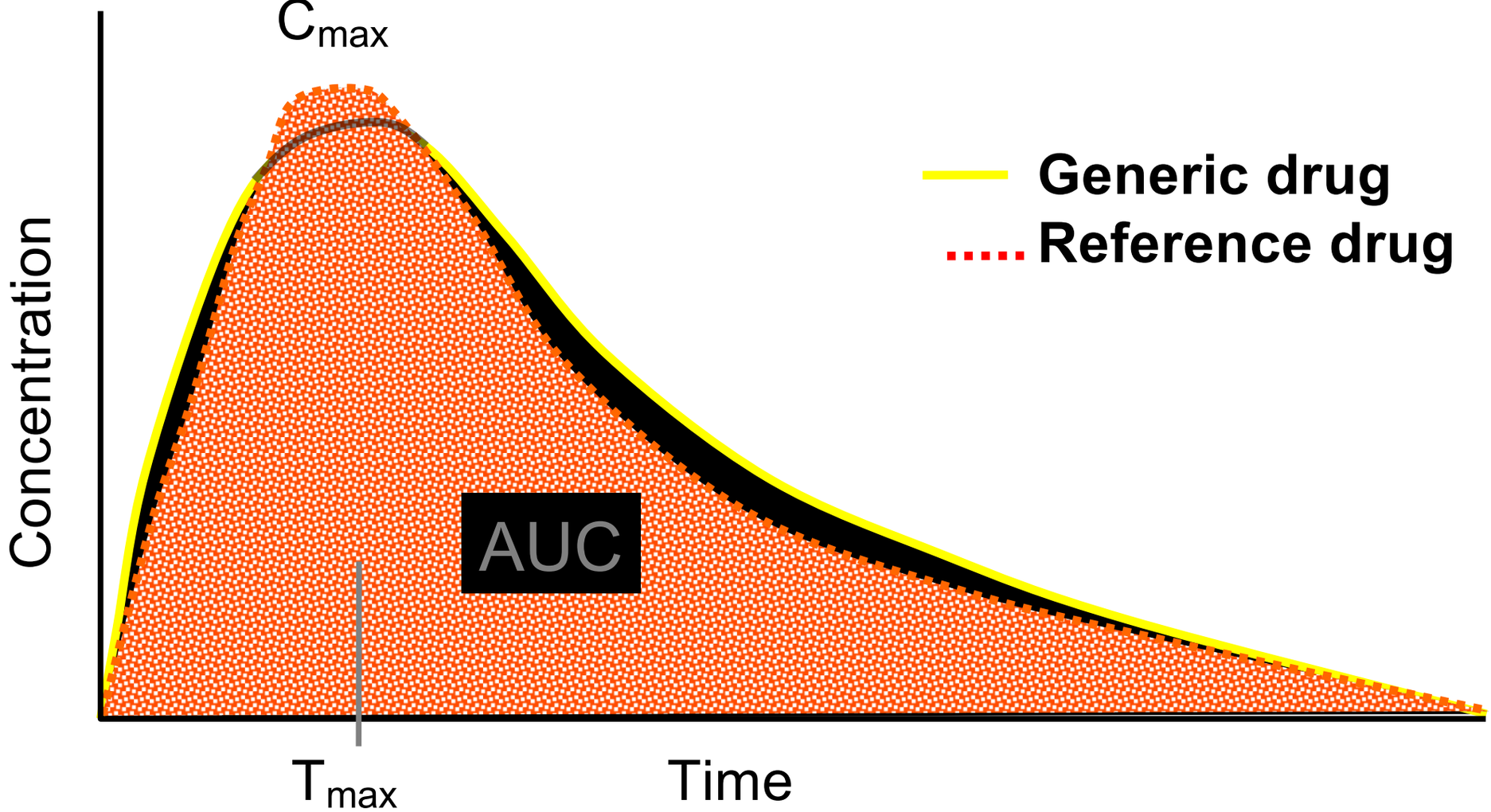
$$F = \frac{AUC_{po}}{AUC_{iv}} \times 100$$



Bioequivalence

Bioequivalence **occurs when two formulations of the same compound have the same bioavailability and the same rate of absorption**

i.e., they have similar AUC, C_{max} and T_{max}



Pharmacokinetic parameters

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Elimination half-life ($t_{1/2}$)

Elimination half-life is the time it takes the drug concentration in the blood to decrease to one half of its initial value after intravascular administration

Unit: time (min, h, day)

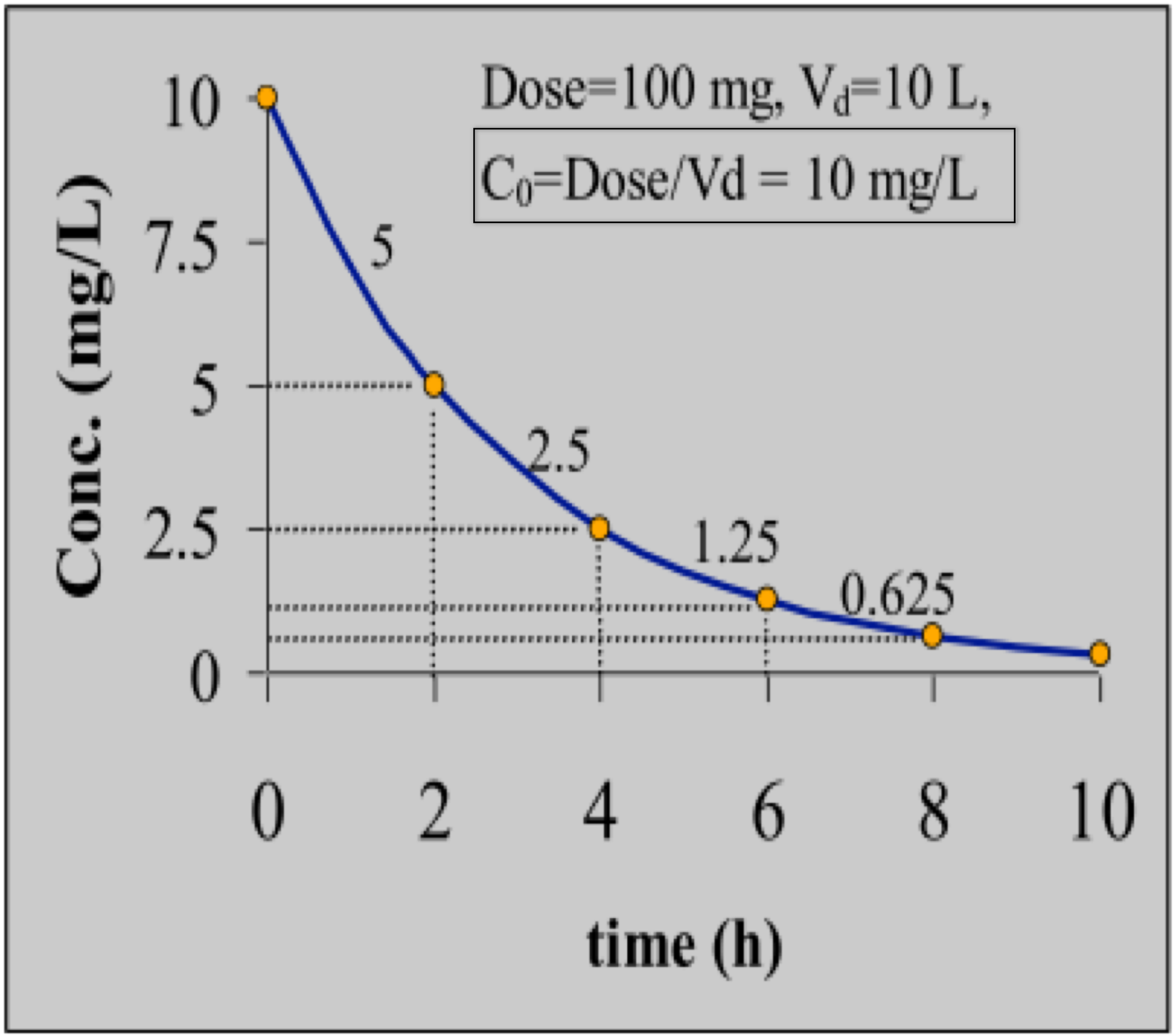
Elimination half-life depends on V_D and Clearance values:

$$Cl = k\,Vd \qquad k = \frac{0.693}{T½}$$

How Vd and Clearance will affect the time of permanence of a drug in the body?

	Vd		
Clearance	Plasma water (3 L)	Extracellular water (12 L)	Total water (42 L)
Partial reabsorbtion (e.g. 30 mL/min)	69 min	277 min	947 min
Glomerular Filtration 130 mL/min	16 min	64 min	219 min
Tubular Secretion 650 mL/min	3 min	13 min	44 min

Rate of elimination: first order kinetic

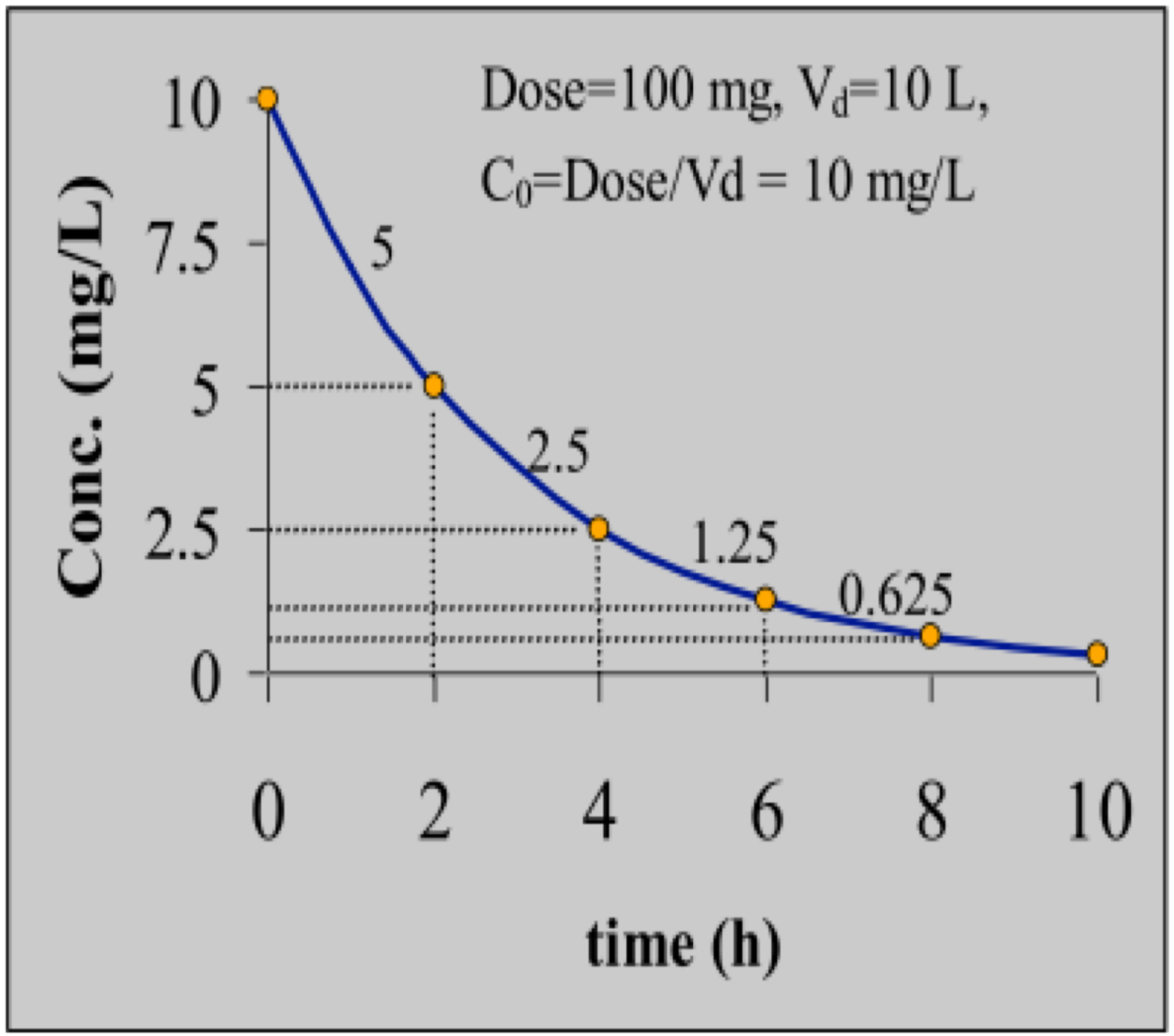


The drug is given i.v. and blood samples are collected at various times to measure the plasma concentrations of the drug

As the drug is eliminated, the plasma concentration of the drug decreases

Rate of elimination: first order kinetic

If the elimination of a drug follows a first-order kinetic



the elimination rate is proportional to plasma concentration

and therefore it decreases with time as the plasma concentration of the drug decreases

Elimination of most drugs administered at therapeutically relevant doses follows a first-order (linear) kinetic

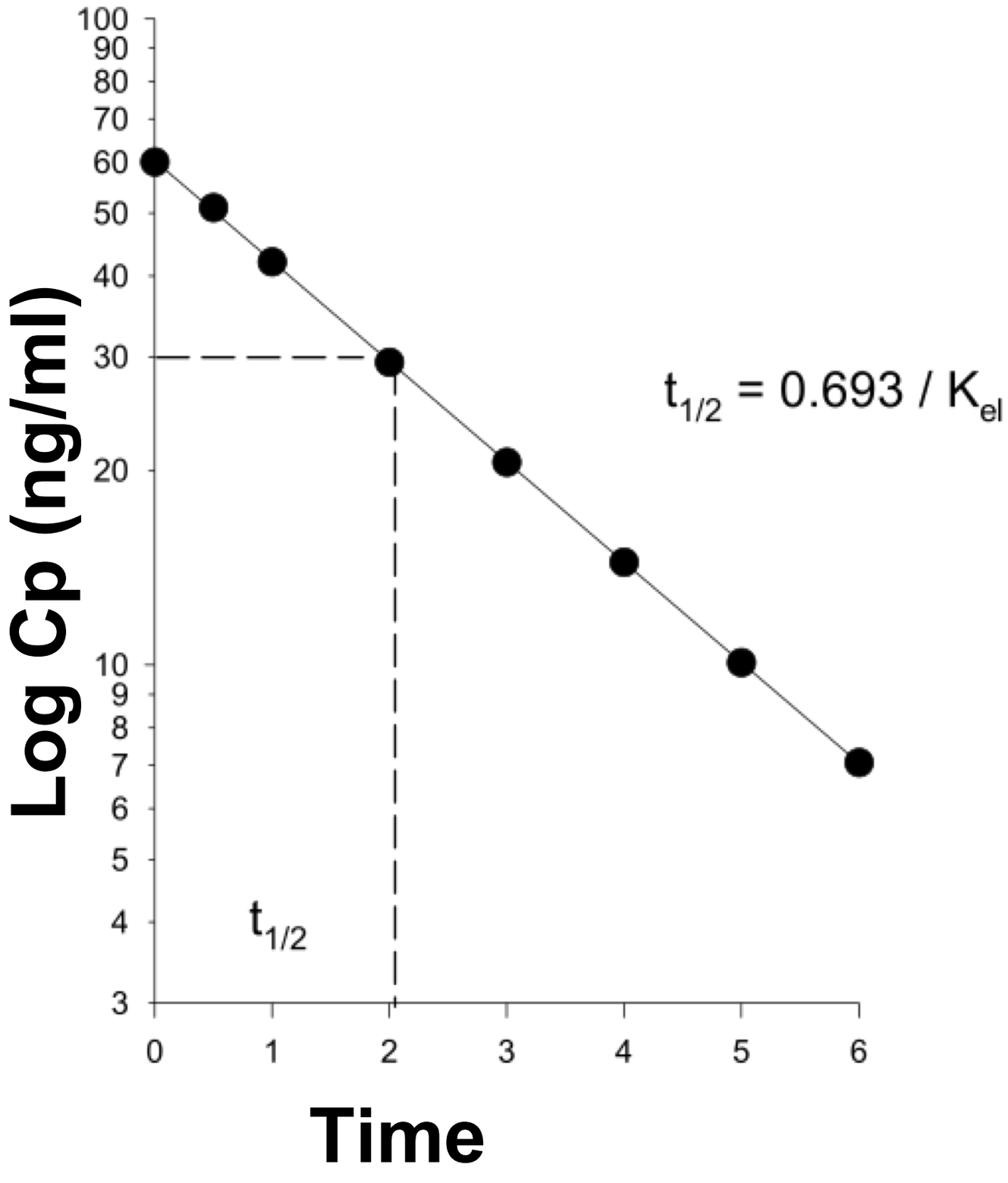
Rate of elimination: first order kinetic

If the elimination of a drug which follows a first-order kinetic

in a semi-log graph a straight line is obtained

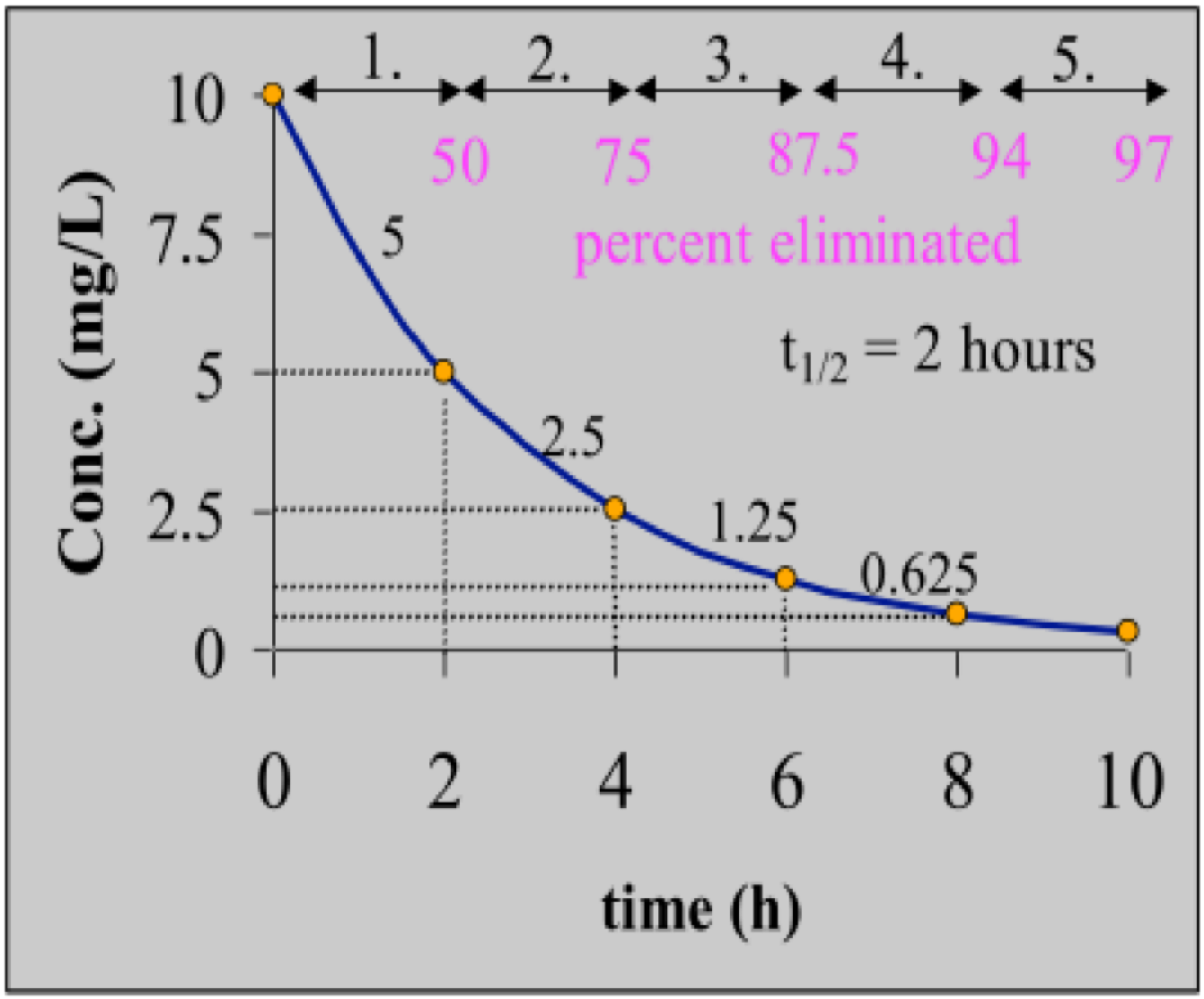
From the slope of the line the k_{el} can be estimated by means of the linear-regression analysis as well as the $t_{1/2}$:

$$t_{1/2} = 0.693 / k_{el}$$



Use of $t_{1/2}$:

$t_{1/2}$ can be used to predict how long it will take for the drug to be eliminated from plasma



The principle of linear pharmacokinetic

Elimination is not saturable (non-capacity-limited) and the rate of drug elimination is directly proportionate to the plasma concentration of the drug (Fick's law!)

Nonlinear (or zero order) pharmacokinetics

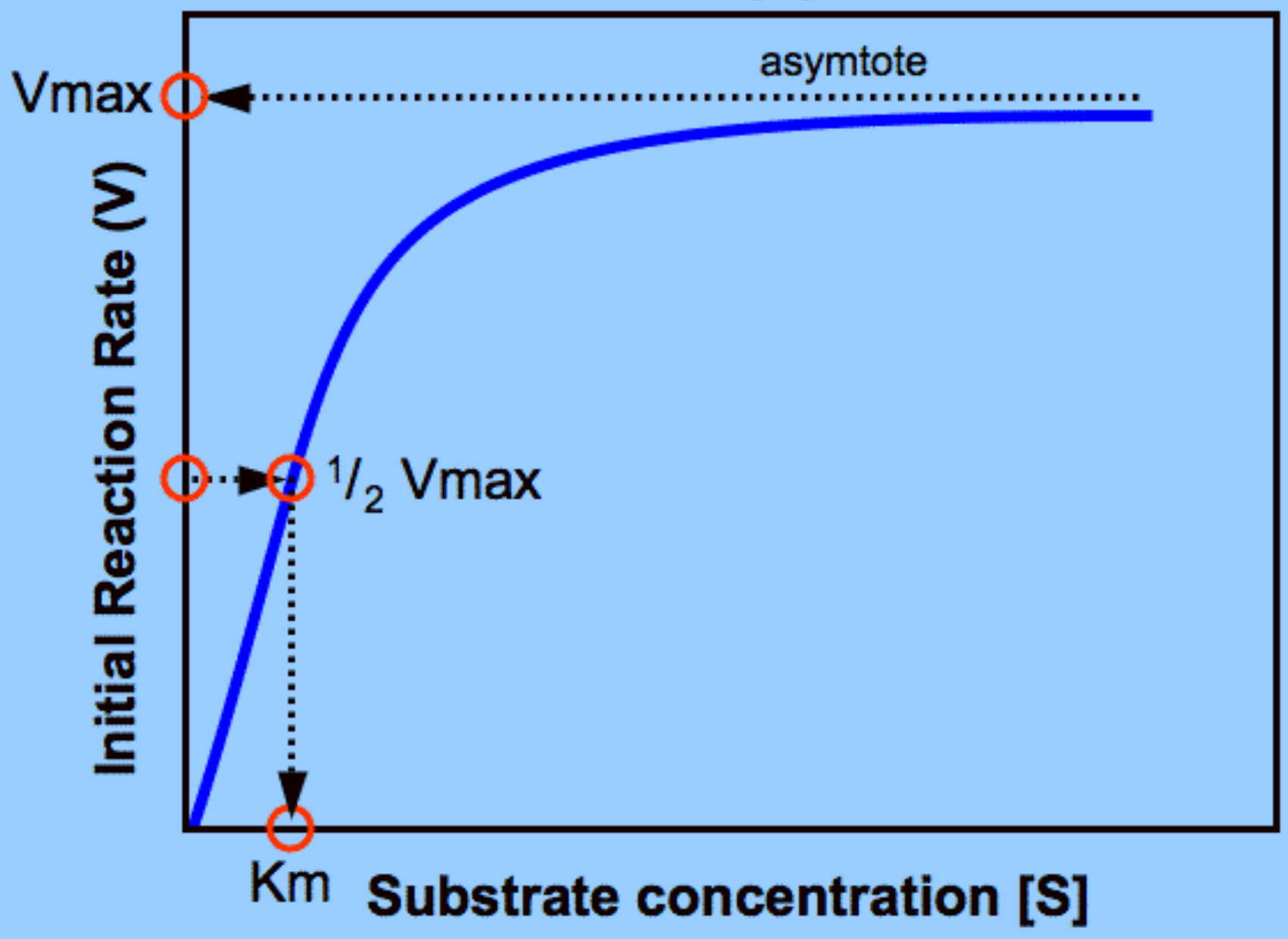
Nonlinear pharmacokinetic is capacity-limited, dose or concentration dependent and saturable
The rate of elimination is constant, irrespective to plasma concentration
No real $t_{1/2}$ can be calculated

$$\text{Rate of elimination} = \frac{V_{max} \cdot C}{K_m + C}$$

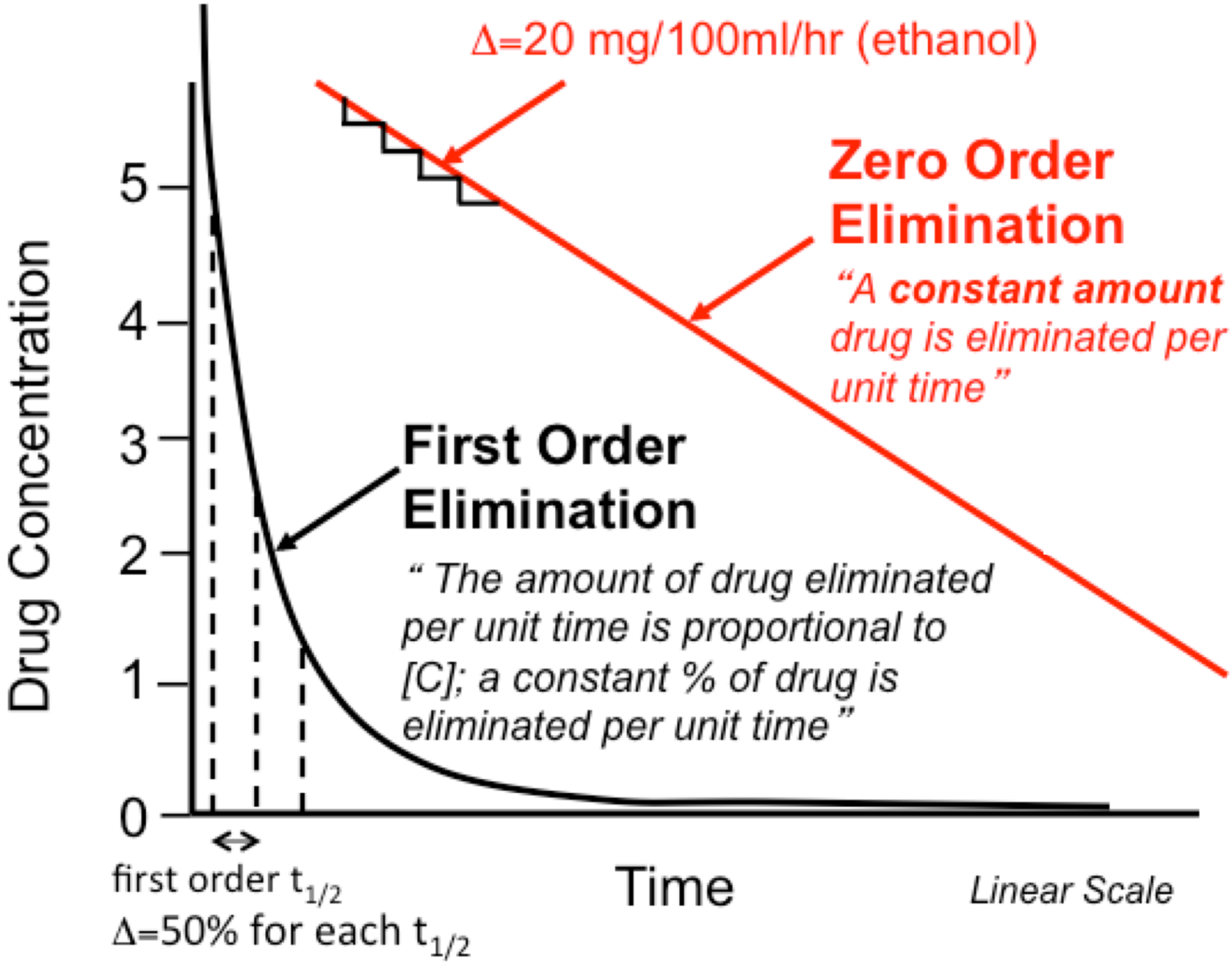
Michaelis- Menten
Examples: ethanol, phenytoin, theofylline

Michaelis Menten Plot

$$V = \frac{Vmax \bullet [S]}{Km + [S]}$$



Nonlinear (or zero order) pharmacokinetics



Nonlinear pharmacokinetics in a semi-log graph