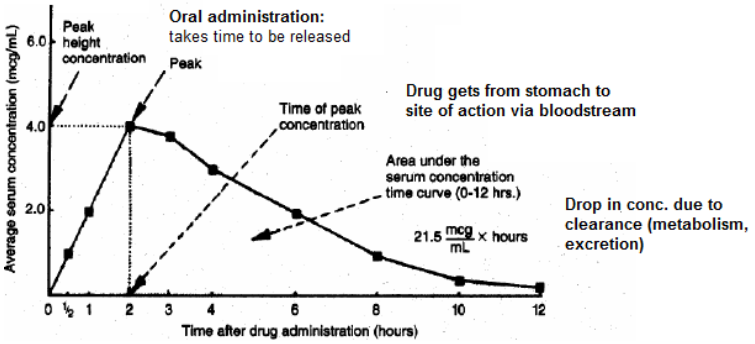
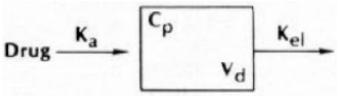
Mono-exponential pharmacokinetics

PK key concerns

- Drug dosage
- Drug plasma concentration
- Peak plasma concentration
- Half life
- Rates (absorption, elimination)



One compartment model



- Hypothetical representation of the body as 'one compartment'
- Assumptions:
  - Volume of each compartment remains constant
  - Drug instantaneously and uniformly distributes throughout the entire compartment
- Zero order kinetics – e.g. 2 molecules/min – number is constant
- First order kinetics – e.g. 2%/min – proportion is constant

Mono-exponential PK assumptions

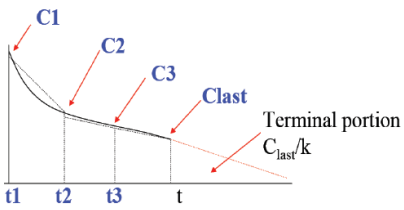
- IV bolus – instantaneous distribution
- First order output/elimination
- One compartment model

Clearance (CL)

- Definition: plasma volume cleared of a drug per unit time (volume/time, e.g. L/h)
- Efficiency of drug elimination from the body – if efficiency is low, decrease the dose
- Used to estimate maintenance dose rate
- Clearance mechanisms (together make the 'total body clearance')
  - Hepatic metabolism (hepatic clearance of drug to an active or inactive metabolite)
  - Renal excretion (renal clearance of a drug unchanged in the urine)
  - Elimination into bile and excreted in faeces

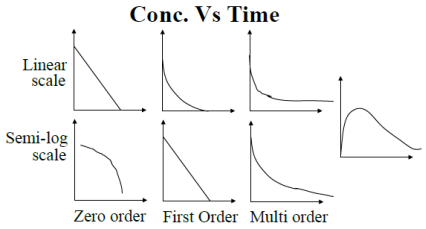
Area under curve (AUC)

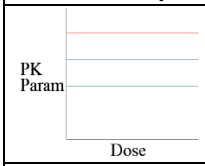
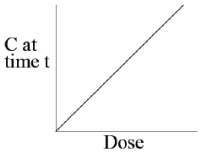
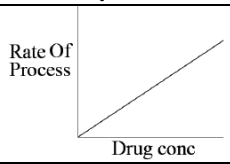
- Area under the plasma concentration vs. time curve
  - Represents total amount of drug absorbed into systemic circulation following administration of a single dose of that drug
- Parameters to consider:
  - Peak height concentration (C_{max})
  - Time of peak concentration (T_{max})
  - Area under the blood/serum/plasma concentration time curve (AUC)
- Calculate AUC using the trapezoidal rule (only for linear/Cartesian graphs)
  - $Area = \frac{1}{2}(A + B) \times H$
  - Terminal log-linear portion ($AUC_{x\text{-}\infty}$) : C_{last}/K_{el}
  - $AUC_{0\text{-}\infty} = AUC_{0\text{-}x} + AUC_{x\text{-}\infty}$
  - Alternatively: $AUC_{0-\infty} = \frac{Dose}{Cl}$
    - AUC = all the amounts eliminated over the duration systemic circulation



PK graphs

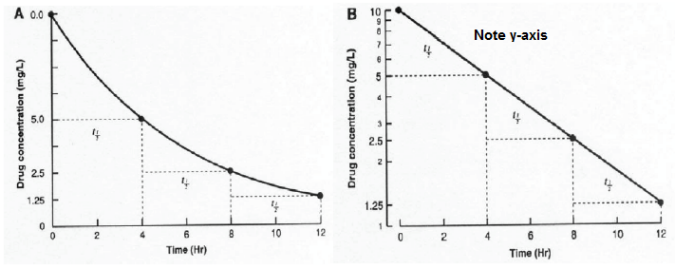
- Independent variables
  - Time
  - Drug dose size
- Zero order: $C_p = {C_p}^0 - K_{el}t$
- First order: $C_p = {C_p}^0 e^{-K_{el}t}$



Dose is independent variable	Dose is independent variable	No independent variable
		
PK parameters do not change with dose – are independent of dose; linear PK	Concentration increases proportionally with dose; drug PK is linear	Rate is low when conc. Is low (driving force is drug conc.); rate is high when conc. Is high

Note: log-linear graph

- 1 cycle = increase by ten-fold
  - E.g. Y-axis: 0.1, 1, 10, 100, 1000 are all spaced evenly apart
- Never start Y-axis with 0 since log(0) does not exist
- If using log-linear graph, the Y-axis is titled C_p (not log(C_p)) since the scale is already logged
- Slope = $\frac{logC_{p2} - logC_{p1}}{t_2 - t_1}$



Linear Scale | Semi-log Scale or Log-linear Scale

PK parameters	Definition	Units	Example
C_p	Drug concentration in plasma	Mass/volume	mg/L
${C_p}^0$	Initial concentration after dosing	Mass/volume	mg/L
V_d	Volume of distribution	Volume	L
K_{el}	Elimination rate constant	$Time^{-1}$	hr^{-1}
CL	Clearance	Volume/time	L/h
t	Time after dosing	Time	min
AUC	Area under curve	$\frac{amount\ of\ drug \times time}{volume\ of\ fluid}$	mg*hour/mL

Mono-exponential PK Equations

Linear	$C_p = {C_p}^0 e^{-K_{el}t}$		
Log-linear (form y=ax+b)	$\log C_p = -\frac{K_{el}}{2.303}t + \log {C_p}^0$	$\ln C_p = \ln {C_p}^0 - K_{el}t$	
AUC	$Area = \frac{1}{2}(A+B)\times H$	Terminal portion = $\frac{C_{last}}{K_{el}}$	$Dose = CL \times AUC_{0-\infty}$
PK parameters	$V_d = \frac{Dose}{{C_p}^0}$	$K_{el} = \frac{0.693}{t_{1/2}}$	$CL = K_{el}V_d$

$\ln X = 2.303 \log X$