Pharmacokinetics

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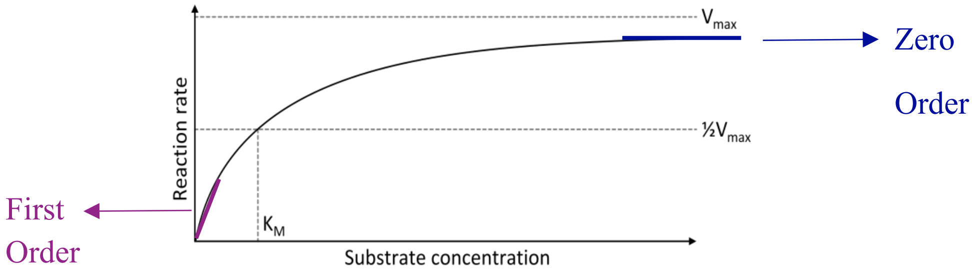
Pharm D. Heba Al-jamal

ARKAN ACADEMY

Rates of Reactions

- The order of a reaction refers to the way in which the *concentration of drugs or reactants* influences ***the rate of a chemical reaction or process***.
- ***Remember:***



- ***Example 1:*** Imagine a bus with a capacity of 100 passengers arrives at a bus stop where 1,000 people are waiting. The bus can only take 100 people, leaving 900 behind. When the next bus arrives, it takes another 100 people. Regardless of whether there are 1,000 or 900 people waiting, the bus always takes the same 100 passengers. In this case, the process is ***zero-order***, where the *rate is* fixed, *independent* of the number of people (or concentration/amount). The rate reaches its maximum capacity.
- ***Example 2:*** If a bus arrives when there's no crowd, and there are only 20, 30, or 5 people waiting, the bus takes all of them. In this case, the *rate depends* on the number of people (or concentration/amount), which means the process is ***first-order.***

- **Zero Order Rates:** refers to a process in which the *rate of reaction* is ***constant*** and ***independent*** of the *concentration* or *amount* of the substance.

- Rate = $\frac{dX}{dt}$ = -Vm (The rate is constant and equals -Vm)
  Xt = Xo – Vmt (X: the amount, Vm: the maximum velocity, t: the time).

- In any reaction: **A ⟶ B**
  - ✓ $\frac{dA}{dt} = -Vm$
  - ✓ $\frac{dB}{dt} = +Vm$

  Why does drug *decrease* in one area but *increase* in another?

- ***Answer:*** This concept is important when we look at ADME processes like absorption. For example, when you administer a drug in tablet form:
  - ✓ If you observe from the GIT side, the amount of the drug *decreases* over time.
  - ✓ But if you look at it from the blood side, the amount is *increasing*.

- This means the same process, when viewed from different perspectives, shows a decrease (negative) from one side and an increase (positive) from the other. The same principle applies to the other processes in **ADME**

Xt : drug amount at any time **Xo:** drug amount at zero time **Vm :** maximum velocity **T:** time **Unit?** Amount/time

- Rate $= \frac{dX}{dt} = -Vm$ → $Xt = Xo - Vmt$ ***How?***

$$\frac{dX}{dt} = -Vm$$

$$dX = -Vm.dt$$

$$\int_0^t dX = \int_0^t -Vm.\,dt$$

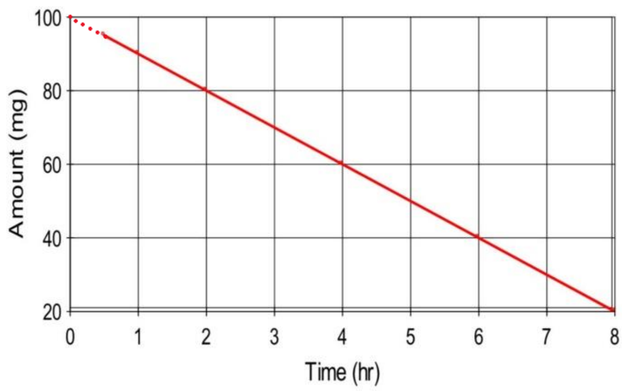
$$\mathbf{X}\Big|_0^t = -Vm\mathbf{t}\Big|_0^t$$

$$X_t - X_0 = -Vm\,(t - 0)$$

$X_t = X_0 - Vmt$ ***What does this mean?***

- *For a certain drug the initial amount from it Xo starts to decrease in zero order rate depending on Vm.*

- **Example:** 100 mg of a drug is given as IV bolus and start to decrease as following:



- ✓ In normal graph paper the zero order is → *linear*
- ✓ The linear equation: **Y = mX + b** , where:
  - **m**: the slope (from any two points)

$$\frac{\Delta Y}{\Delta X} = \frac{80-60}{2-4}$$

$$= \frac{20}{-2} = -10 \text{ mg/hr}$$

  - **b**: the Y-intercept = 100 mg
- ✓ So the equation → **Xt = 100 -10t**

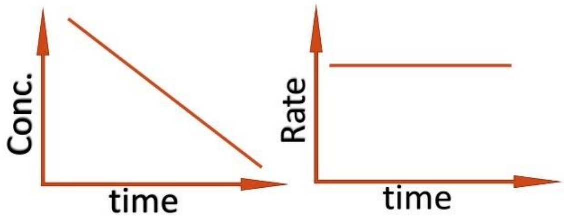
- **Questions:**
  - ✓ **According to this equation what is the amount in the body after 4 hr?**
    Xt = 100 – 10*4
    Xt = 100 – 40
    Xt = 60 mg
  - ✓ **What is the eliminated amount after 4 hr?**
    After 4h the drug amount in the body 60 mg, so the eliminated:
    100 – 60 = 40 mg

- ✓ **What <u>time is</u> required for the amount to drop to <u>60 mg</u>?**
  60 = 100 – 10t
  -40 = -10t
  t = 4 hr

- ✓ **Half-life? (Time needed for any amount or conc to drop to it's half)**
  Time from 100 mg to 50 mg
  50 = 100 - 10t
  t = 5 hr

➢ In zero order reactions half life is <u>useless</u> (depends on the initial amount).

- ***Charts of Zero Order:***



- **First order rates**: refers to a process where the *rate of reaction* is ***directly proportional*** and ***dependent*** on the *concentration* or *amount* of the substance.

➢ Rate = $\frac{dX}{dt}$ = - KX (The rate depends on the amount X).

lnX = lnXo – Kt (<u>X</u>: the amount, <u>K:</u> constant, <u>t</u>: the time).

Xt = Xo e^{-Kt} **How?**

➢ Rate ∝ Amount , to remove proportionality sign, replace it with (=) and multiply by a constant.

Rate **= K**X

$\frac{dX}{dt}$ = - KX (Units: **K**: 1/time, **X**: amount)

$\frac{dX}{X}$ = - K.dt

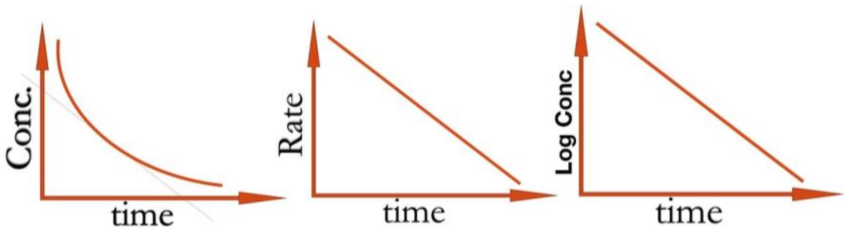
$\int_0^t \frac{dX}{X} = \int_0^t -K.dt$

$lnX \Big|_0^t = -Kt \Big|_0^t$

*ln*Xt – *ln*Xo = -K(t – 0)

*ln*Xt = *ln*Xo – Kt (This equation is ***<u>linear</u>*** between <u>*ln*(amount)</u> & <u>time</u>.

- ***Charts of First Order:***



- ***In first order kinetics, how do we remove the natural logarithm (ln)?***

$ln Xt - ln Xo = -Kt$ (logarithmic equation)

$ln \frac{Xt}{Xo} = -Kt$ (take **e** to the both sides)

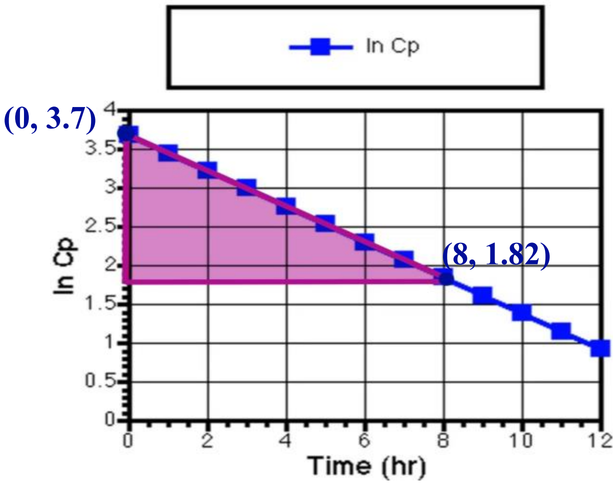
$$e^{ln\frac{Xt}{Xo}} = e^{-Kt}$$

$$\frac{Xt}{Xo} = e^{-Kt}$$

$Xt = Xo\, e^{-Kt}$ (Exponential equation)

- **The half-life for the first order reaction is constant:** $t_{0.5} = \frac{0.693}{K}$

➢ **Example:**



➢ **Write down linear relationship for the plot: (Y = b + mX)**

b: the Y-intercept = 3.7

m: the slope $= \frac{lnC1 - lnC2}{t1 - t2}$

$$= \frac{3.7 - 1.82}{0 - 8} = -0.235 \text{ hr}^{-1}$$

X: the time

So, the linear equation → **Y= 3.7 – 0.235t**

➢ **Write the equation in exponential form: ($Ct = Co\, e^{-Kt}$)**

Take (e) for both sides:

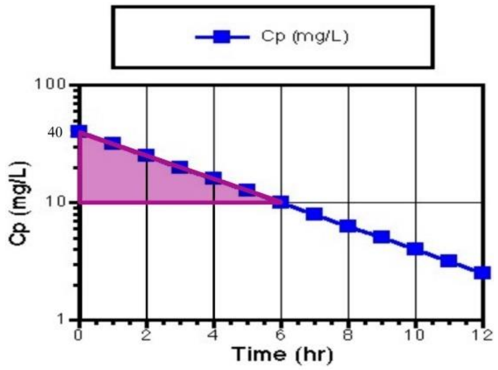
$Ct = 40.4\, e^{-0.235t}$

➢ **What is the conc after 4 hours?**

✓ At time 4 hrs we have a value of approximately 2.7, but this is **NOT conc**! It's the Ln of conc.

✓ So we have to find **anti-Ln** (using e) to find the conc, this extra step can increase the chance of mistakes in calculation.

- **Is there another way to get a <u>linear result</u> without using log?**
  - ✓ Yes, you can replace normal paper with <u>semi-log paper</u>, and this way the values will appear <u>linear</u> *without* needing to take the <u>anti-ln.</u>
  - ✓ ***Semi-log paper:*** A graph in which one of the scales is <u>normal (X)</u> and the other is <u>logarithmic(Y)</u>



- **How to obtain the equation parameters from semi-log paper? *($Ct = Co\ e^{-Kt}$)***

Co = b = Y-intercept

Co = 40 mg/L

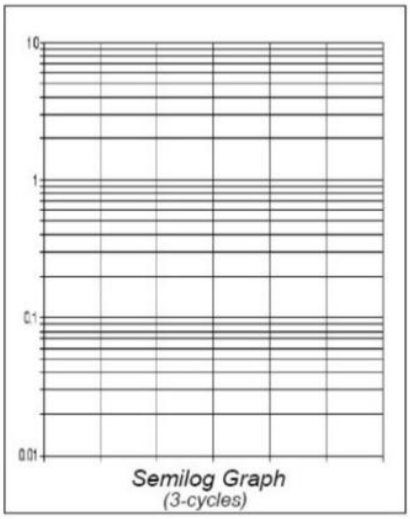
Slope = **-K** = $\frac{\ln 40 - \ln 10}{0-6}$

-K = -0.23 hr $^{-1}$

- ✓ The ***<u>Exponential</u>*** equation: $Ct = 40\ e^{-0.23t}$
- ✓ The ***<u>logarithmic</u>*** equation: *ln*C = *ln*(40) – 0.23t

  *ln*C = 3.7 – 0.23t

- ***So semi-log paper helped me saving the values without converting them to anti-log/Ln.***
  - The ***semi-log scale*** is characterized by:
    - ✓ <u>Uneven spacing</u> between units within a cycle *(starting far apart and then getting closer).*
    - ✓ <u>But the distance</u> from the beginning to the end of each cycle is the same between cycles.
  - The ***idea behind logarithmic transformation*** is that *large numbers*
  - become <u>closer</u> to each other, while *small numbers* <u>spread further apart</u>.
    - ✓ If we imagine it on a ***concentration vs. time graph*** for ***first-order kinetics***:
      - <u>Initially</u> (with large numbers) the *decline is <u>rapid</u>*.
      - <u>Later</u> (with small numbers) the *decline is <u>slower</u>*.
      - When we transform the values *to log graph*, the curve becomes *more linear*.



  - ***How is this useful?*** If we imagine the <u>following numbers:</u> 1/10/100/1000/10000, are the differences between them equal?
    - ✓ No, the differences are ***<u>not equal</u>,*** because the difference between 1 and 10 is 9, while the difference between 10 and 100 is 90, and so on.
    - ✓ **<u>But</u>** if you take the **<u>logarithm</u>** of these values: 0/1/2/3/4, the differences become equal = 1.

TABLE 2-4.
First-Order Elimination

Time after Drug Administration (hours)	Amount of Drug in Body (mg)	Amount of Drug Eliminated Over Preceding Hour (mg)	Fraction of Drug Eliminated Over Preceding Hour
0	1000	—	—
1	880	120	0.12
2	774	106	0.12
3	681	93	0.12
4	599	82	0.12
5	527	72	0.12
6	464	63	0.12
7	408	56	0.12

- **The First Order**:
- ✓ The **amount** lost → not contant, depends on the conc.
- ✓ The **fraction** lost → constant.

TABLE 2-5.
Zero-Order Elimination

Time after Drug Administration (hours)	Amount of Drug in Body (mg)	Amount of Drug Eliminated Over Preceding Hour (mg)	Fraction of Drug Eliminated Over Preceding Hour
0	1000	—	—
1	850	150	0.15
2	700	150	0.18
3	550	150	0.21
4	400	150	0.27
5	250	150	0.38

- **The Zero Order**:
- ✓ The **amount** lost → contant, conc independent.
- ✓ The **fraction** lost → not constant.

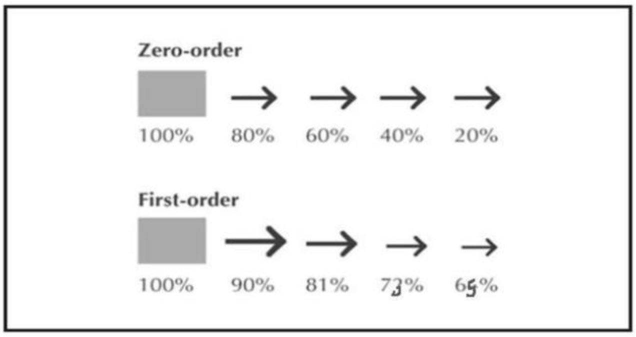


FIGURE 2-7.
Zero- versus first-order elimination. The size of the arrow represents the amount of drug eliminated over a unit of time. Percentages are the fraction of the initial drug amount remaining in the body.

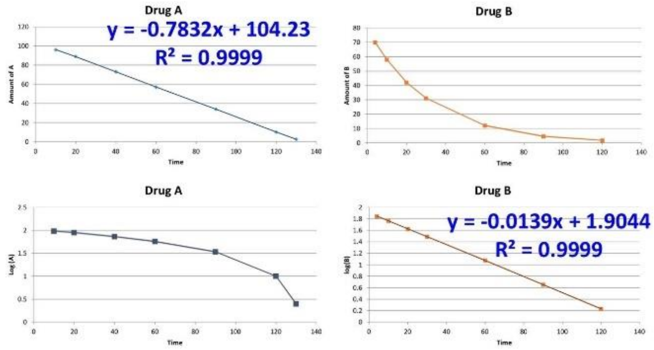
- ➢ ***Zero-order kinetics***: the same ***amount*** of the dose is ***eliminated*** each time, regardless of the initial amount, meaning the **rate is constant**. In the example above, we started with 100, then it became 80, then 60, and so each time, 20% was eliminated.
- ➢ ***First-order kinetics:*** a ***fraction*** of the current amount is ***eliminated***, so the rate is not constant.
- ➢ In the example, we started with 100, which became 90, meaning 10% of 100 was eliminated. Then from 90, it became 81, meaning 10% of 90 was eliminated, and so on… each time, 10% of the last concentration is eliminated. This means the **rate here is concentration-dependent.**

- **Example:** Plot the following data both on semi-log graph and standard rectangular coordinates, and then answer the following:
  - ➢ Does the decrease in the amount of drug A, B appear to be a **zero-order** or a **first-order** process?
  - ➢ What is the rate constant k?
  - ➢ What is the half-life t1/2?
  - ➢ What is the equation for the line produced on the graph?

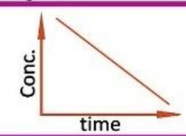
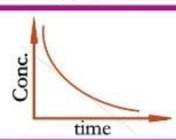
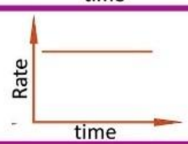
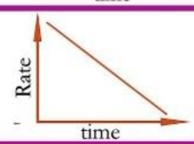
Time (min)	Drug A mg
10	96
20	89
40	73
60	57
90	34
120	10
130	2.5

Time (min)	Drug B (mg)
4	70
10	58
20	42
30	31
60	12
90	4.5
120	1.7

- **Answers:**



	Drug A	Drug B
Order of elimination	Zero-order	First-order
rate constant	The rate itself is constant	0.032 min^{-1}
Half-life	Amount-dependent	21.6 min
Initial amount	104.2 mg	80.2 mg
Equation of the line	A=104.2-0.78t	$B=79.4*e^{-.032t}$

	Zero order	First order
Rate	Constant	Depends on the initial amount/ concentration.
Equation	$X = Xo - Vmt$	$X = Xo * e^{-kt}$
Half-life	$t_{0.5} = Xo/(2*Vm)$ *depends on the Xo	$t_{0.5} = 0.693/k$ *constant
Conc vs time		
Rate vs time		

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+962 790408805