

Physical Pharmacy

Chemical kinetics and stability

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- chemical kinetics: concerned with reaction **rates** and **the sequence of steps by which reaction occurs**.
 - **Rate of reaction** for a given chemical change is the speed with which its reactants disappear and its products form.
 - The sequence of steps by which reaction occurs is called the **mechanism of the reaction**.

$$\textit{Rate} = \frac{-\Delta[\textit{Reactnat}]}{\Delta t} = \frac{\Delta[\textit{Product}]}{\Delta t}$$

Reaction mechanism

- Observe the below reaction: it might look like a single step reaction



- However through experiment, it is suggested that the reaction takes place by a two-step mechanism:

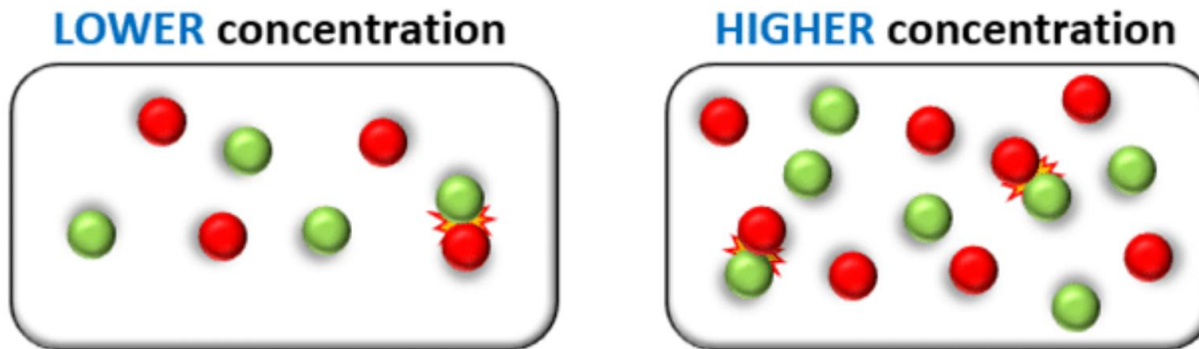
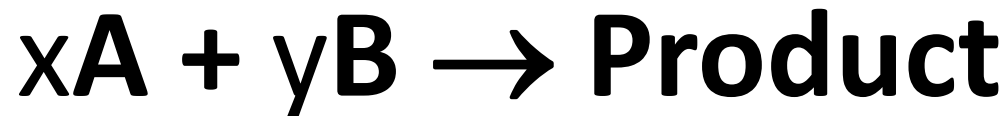


- The chemical equation for an elementary reaction is a description of an individual molecular event that involves the breaking and/or making of chemical bonds (**molecularity**).

Reaction mechanism

- One of the elementary steps is often much **slower** than the others.
- This slowest step is called **the rate-determining step** which is the step that limits the rate at which reactants can be converted to products.
- The overall reaction cannot occur faster than the speed of the rate-determining step.

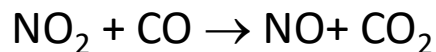
Order of reactions



$$\text{Rate} \propto [\text{A}]^x [\text{B}]^y$$
$$\text{Rate} = k[\text{A}]^x [\text{B}]^y$$

- where k is the rate constant and exponent (x) and (y) represent the order of reaction according to each reactant.
- When we have more than one reactant, the overall order of the reaction is the sum of the exponents.

Order of reaction, exponents, and coefficients



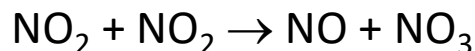
Overall reaction

Rate = $k[\text{NO}_2][\text{CO}]$ (WRONG)

Rate = $k[\text{NO}_2]^2$ (CORRECT)

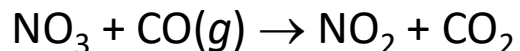
WHY?

Because:



Elementary reaction Slow

Rate = $k[\text{NO}_2]^2$ (✓)



Elementary reaction Fast

Rate = $k[\text{NO}_3][\text{CO}]$ (✓)

- In the overall reaction equation the order of reaction according to each reactant is not equal to the coefficients in the balanced equation:
- In elementary reactions the order of reaction according to each reactant is equal to the coefficient of that reactant in the balanced equation. **(Molecularity)**
- The rate law for the overall reaction depends on the rate law of the rate determining step and the steps preceding it.

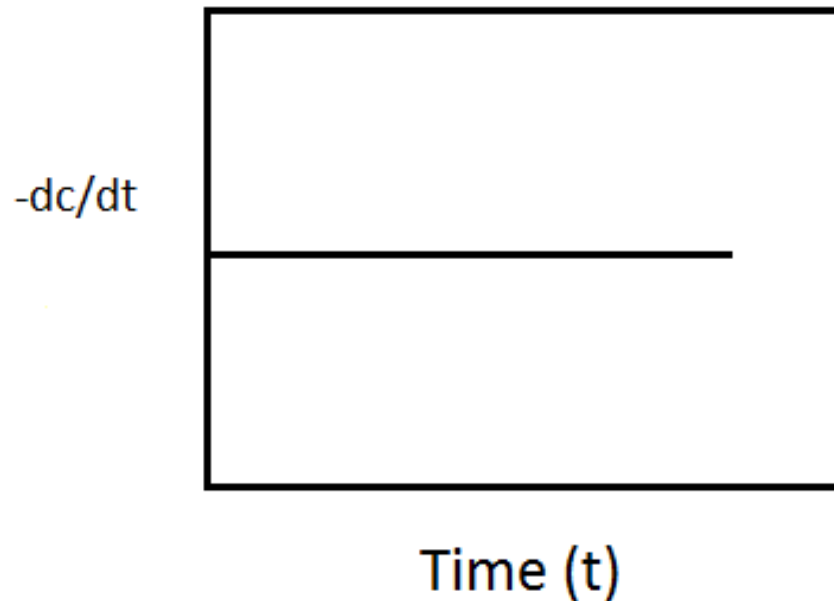
Two important terms: Shelf-life and Half-life

- **Shelf life:** is the time during which the medicinal product is predicted to remain fit for its intended use under specified conditions of storage.
 - In terms of drug degradations it is the time from manufacture or preparation until the original potency or content of the active ingredient has been reduced by 10% [t_{10} or t_{90}].
- **Half-life:** is the time required for one-half of the material to disappear.



Zero order reactions

- Rate is independent of the concentration of the reacting substance remaining.
- The rate of change is constant.
- Examples: Photochemical degradation (e.g. chlorpromazine), metabolism of alcohol in body...



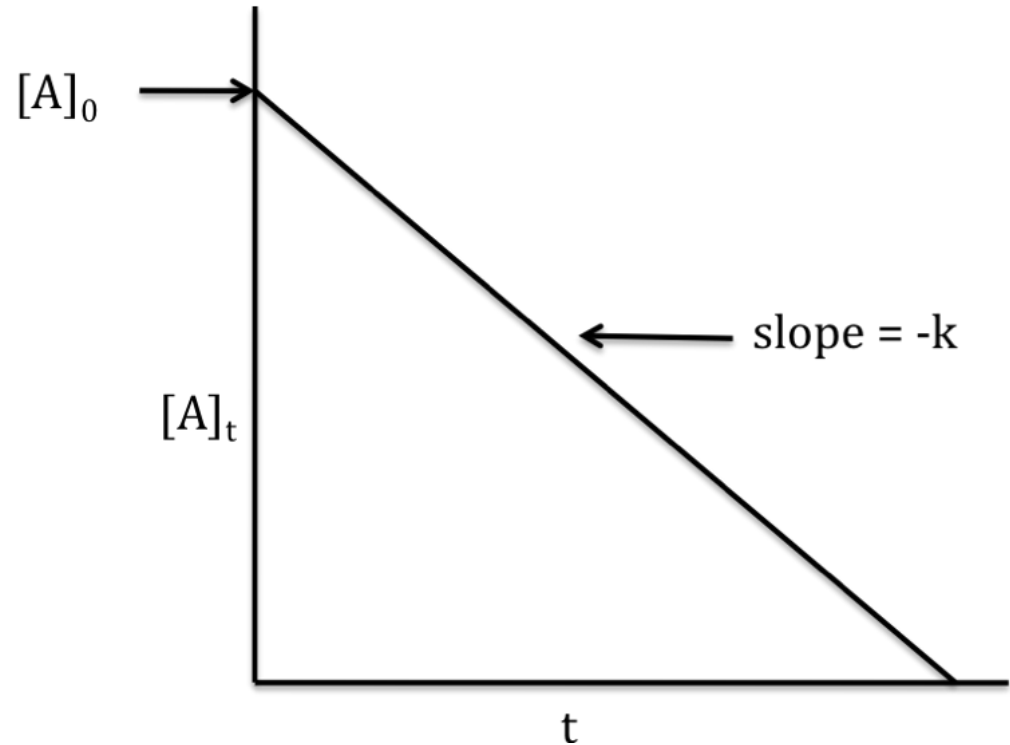
$$-\frac{dC}{dt} = k_0$$

Zero order reactions

- The relationship between time and concentration of the reactant is a **straight line**

- $C_t = C_o - k_o t$

$$t = \frac{C_o - C_t}{k_o}$$



Zero order reactions – Half life and shelf life

- Because the half-life ($t_{1/2}$) is the time required for one-half of the material to disappear, in the present case, after one half, the concentration becomes $1/2C_0$.

$$t_{1/2} = \frac{1/2 C_0}{k_0}$$

For shelf life

$$t_{90\%} = \frac{C_0 - 0.9C_0}{k_0}$$

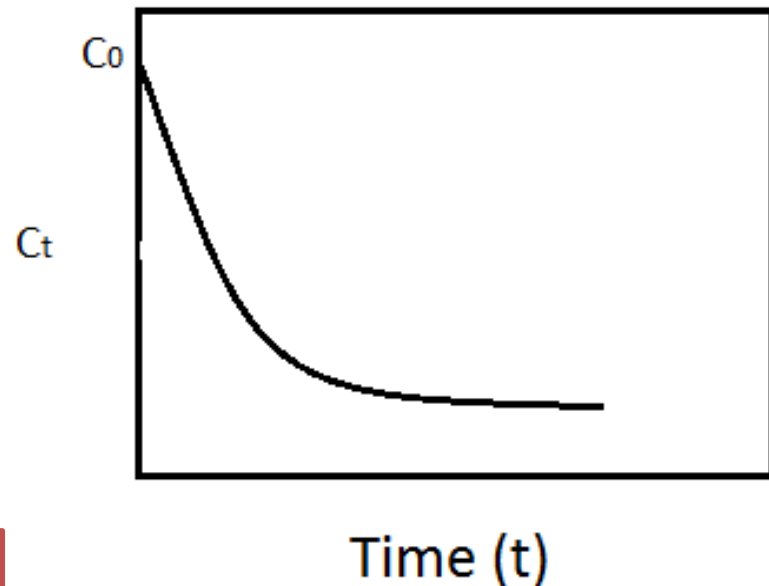
First order reactions

- Rate of reaction is proportional to the concentration of the reactant remaining in the reaction mixture at any time.
- Examples: Degradation of aqueous solutions of many drugs (e g aspirin) and Degradation in some solid or semi solid dosage forms, radioactive decay...

- The rate equation is written:

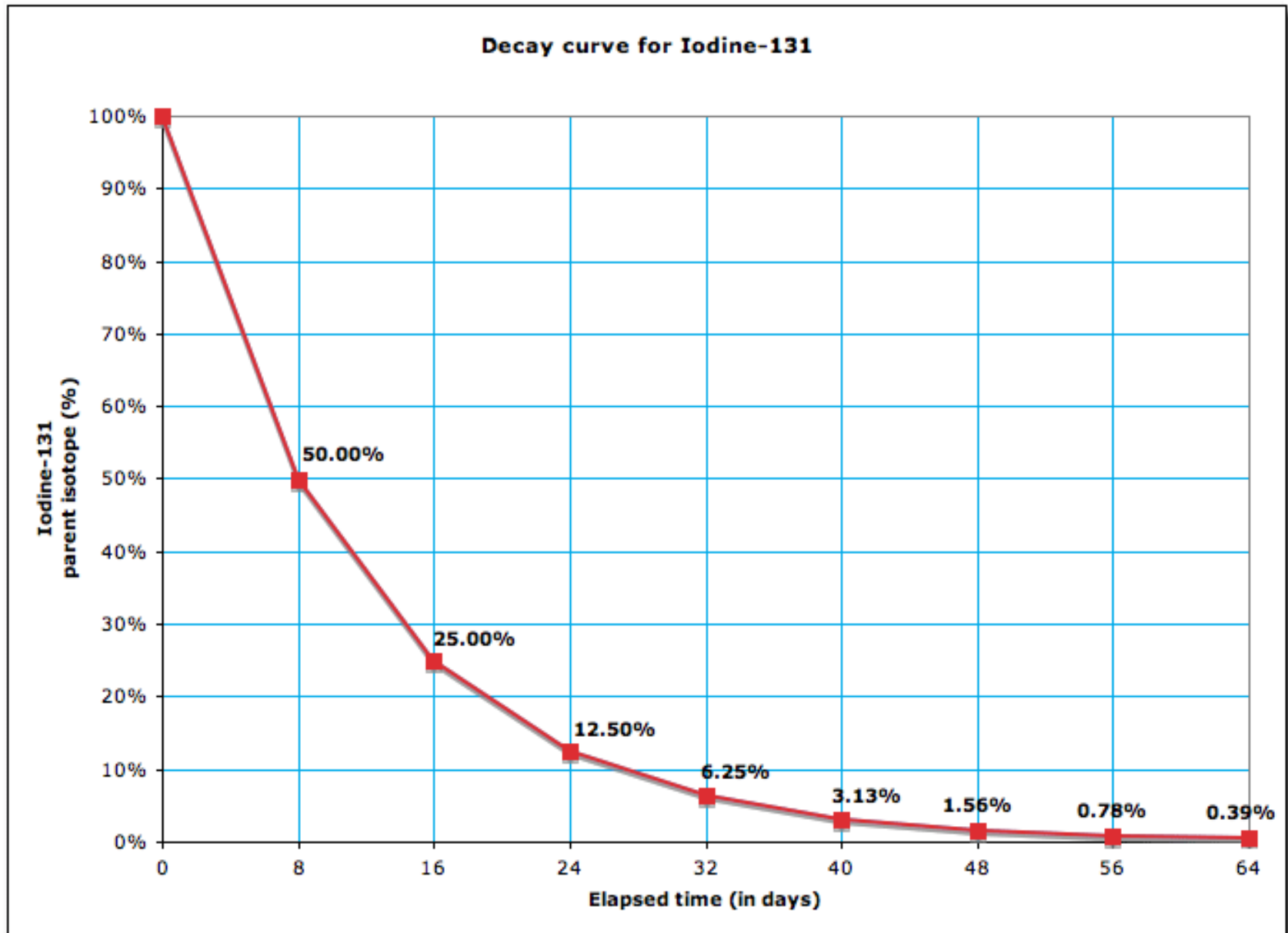
$$-\frac{dC}{dt} = k C$$

- Relationship between concentration and time



What is the unit for First order rate constant?

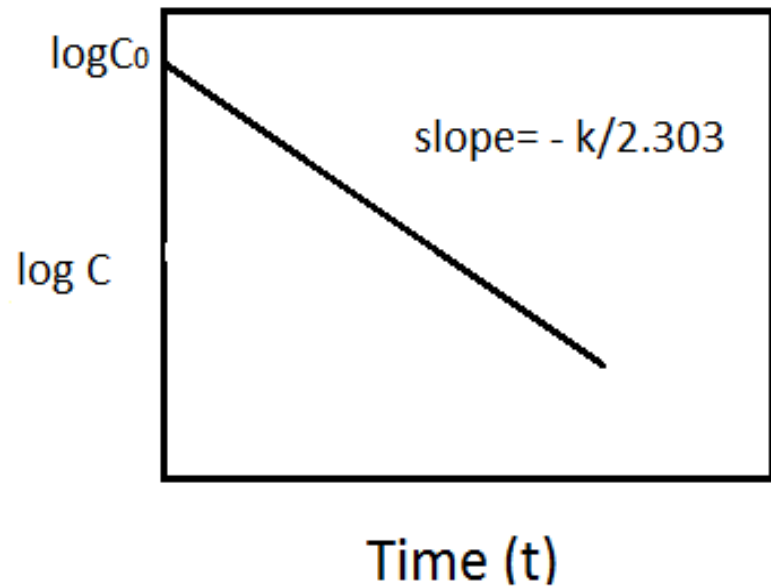
First order reactions



First order reactions

$$-\frac{dC}{dt} = k C \quad \longrightarrow \quad \log C = \log C_0 - \frac{k}{2.303} t$$

We will try to construct a straight line to be able to predict the amount of the drug remaining at a definite time



First order reactions - Half life and shelf life

- To calculate half life and shelf life

$$t_{1/2} = 0.693/k$$

$$t_{90} = 0.105/k$$

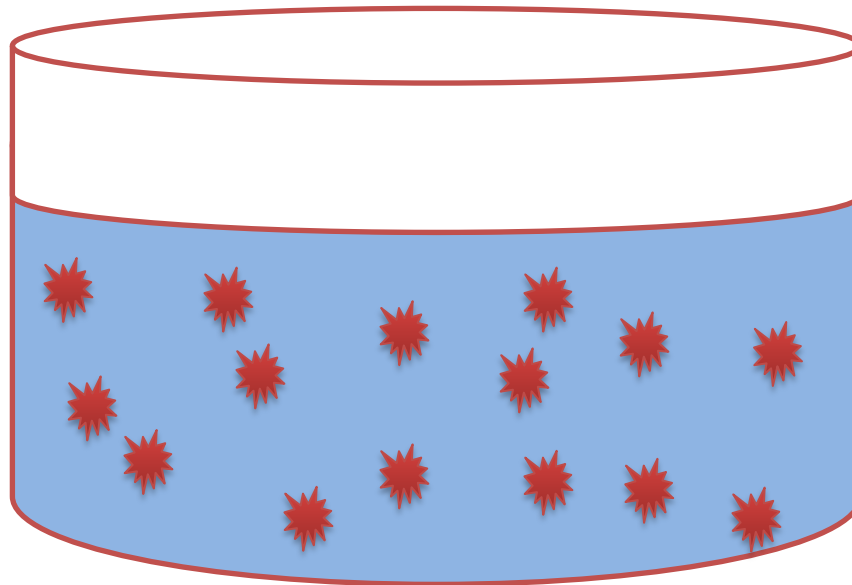
Aspirin has been found to be most stable at pH 2.5 where the first-order rate constant is $5 \times 10^{-7} S^{-1}$ at 25°C. What is the half-life of the reaction?

$$t_{50\%} = 0.693/K_1$$

$$t_{50\%} = \frac{0.693}{5 \times 10^{-7}} = 1.39 \times 10^6 S = 16 \text{ days}$$

Suspensions, Apparent Zero-Order Kinetics

- Suspensions are another case of zero-order kinetics, in which the concentration in solution depends on the drug's solubility.
- As the drug decomposes in solution, more drug is released from the suspended particles, so that the concentration remains constant.



Suspensions, Apparent Zero-Order Kinetics

- The equation for an ordinary solution, with no reservoir of drug to replace that depleted, is the first-order expression, equation
 - $-d[C]/dt = k_1[C]$ where C= concentration of drug in solution = solubility
 K_1 = first order rate constant of solution
- When the concentration [C] is rendered constant, as in the case of a suspension, we can write
 - $K_1[C] = K_0$ where K_0 = zero order rate constant of suspension
- Thus, $K_0 = K_1 \times \text{Solubility}$

Second-Order Reactions

- The rates of bimolecular reactions, which occur when two molecules come together, are frequently described by the second-order equation.
- $A + B \longrightarrow \text{Products}$ (elementary reaction)
- $2A \longrightarrow \text{Products}$ (elementary reaction)
- When the speed of the reaction depends on the concentrations of A and B with each term raised to the first power, the rate of decomposition of A is equal to the rate of decomposition of B, and both are proportional to the product of the concentrations of the reactants:

$$-\frac{d[A]}{dt} = -\frac{d[B]}{dt} = k [A][B]$$

When the initial concentrations of A and B are equal, the rate equation is

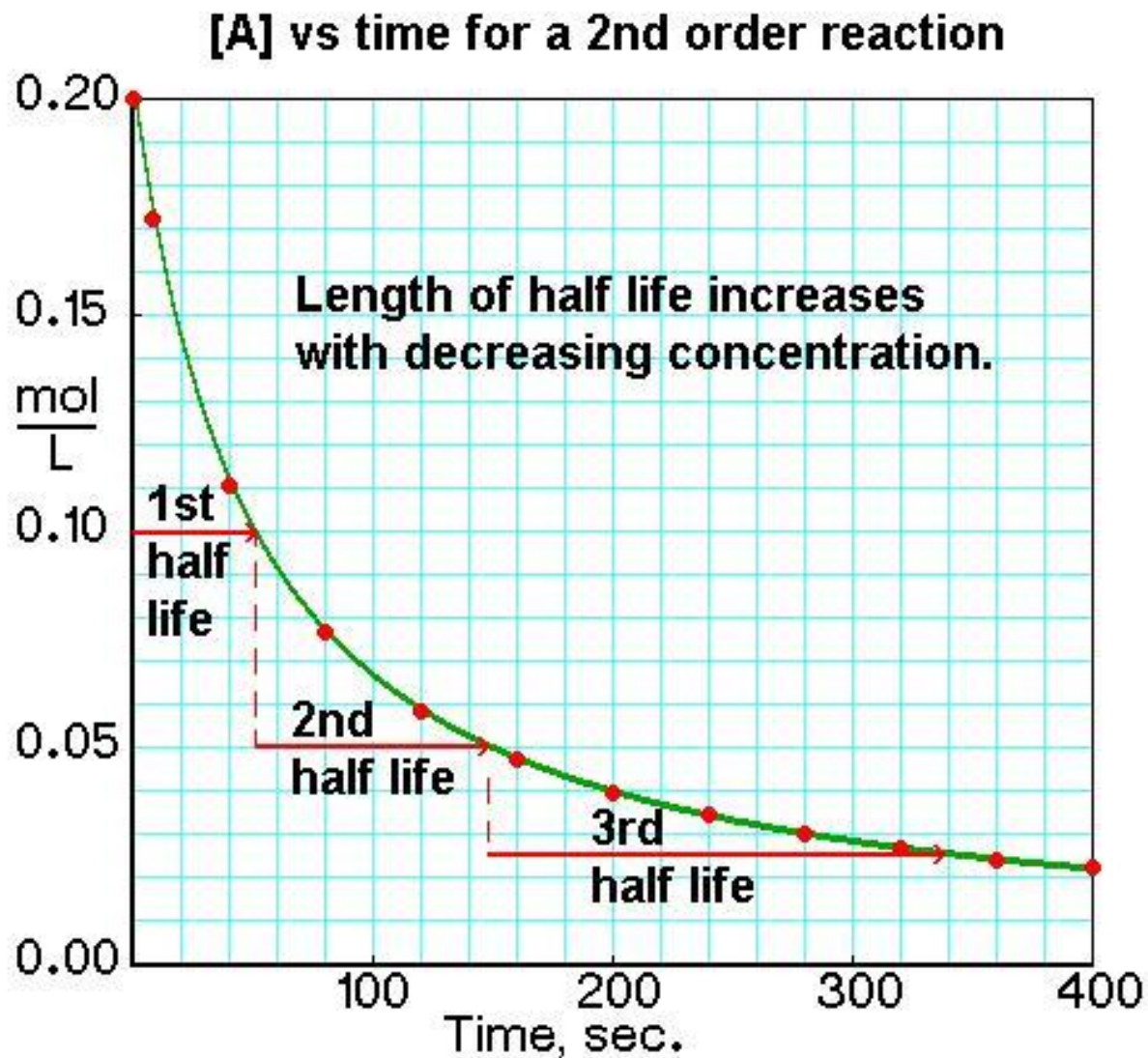
$$\mathbf{Rate = K_2[A]^2}$$

The integrated rate equation is

$$\frac{1}{[A]_t} = \frac{1}{[A]_0} + K_2t$$

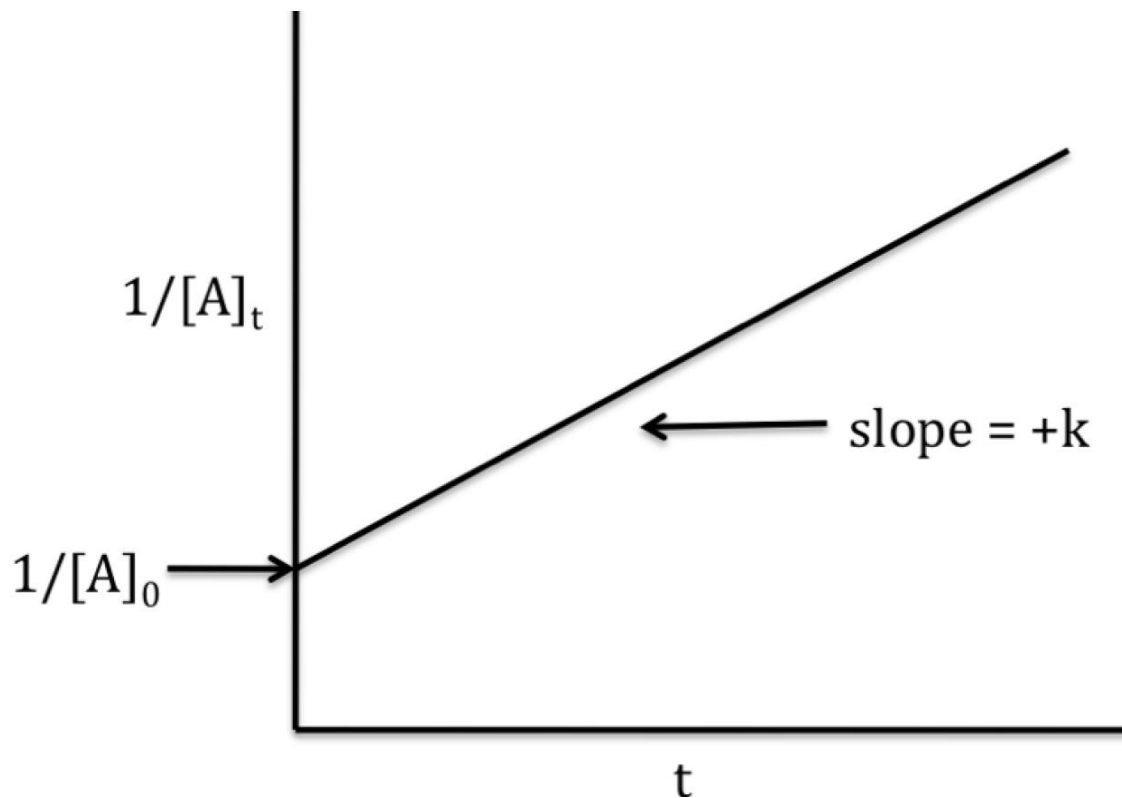
K_2 Second order rate constant (unit is *concentration*⁻¹*time*⁻¹)

Second-Order Reactions



$$\frac{1}{[A]_t} = \frac{1}{[A]_0} + K_2 t$$

A plot of $1/[A]_t$ against t is linear with a slope of K_2 and an intercept of $1/[A]_0$

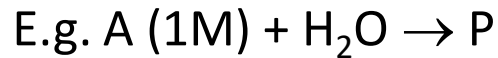


Second-Order Reactions

- The half-life of second-order reaction depends on initial reactant concentrations.
- The half-life is inversely proportional to the initial concentration of the reaction.
- **Half life ($t_{1/2}$) = $\frac{1}{k * \textit{initial concentration of the reactant} [A^{\circ}]}$**
- **$(0.9) = \frac{0.11}{k * \textit{initial concentration of the reactant} [A^{\circ}]}$**
- E.g.: the decomposition of gaseous hydrogen iodide.

Apparent First-Order Reactions

If there are two reactants and one is in large excess, the reaction may still follow first-order kinetics because the change in concentration of the excess reactant is negligible.



Concentration of water is very high (55.5 M), compared to the concentration of A (1 M); therefore, the change in water concentration is negligible compared to that of A.

$$\text{Rate} = k_2[A][H_2O] = k_1[A]$$

$k_1 = k_2[H_2O]$ is the observed pseudo first-order rate constant. This type of reaction is called a pseudo first-order reaction.

Factor affecting reaction rate.

1. Concentration: depends on the order of the reaction based on each reactant.

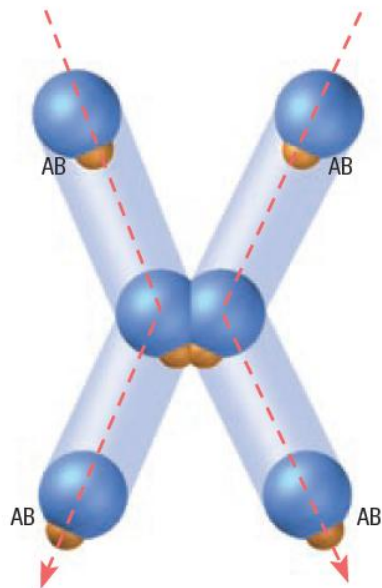
2. **Temperature effect**

What does this mean?

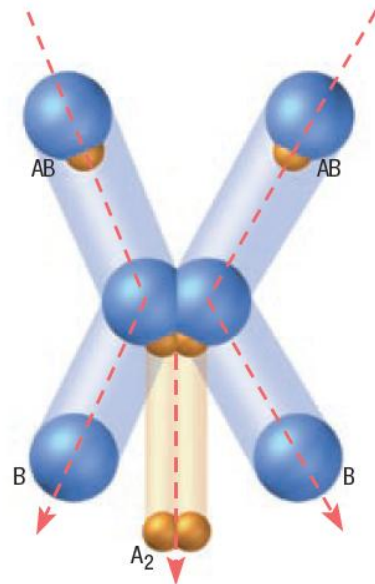


- **Collision Theory:** Reaction rates are expected to be proportional to the number of collisions (**effective collisions**) per unit time. Because the number of collisions increases as the temperature increases, the reaction rate is expected to increase with increasing temperature.
- **Transition state theory: Activation energy:** Chemical reactions must go over an energy barrier called activation energy before a reaction can take place
Activation energy E_a is the minimum amount of energy required to initiate a chemical reaction

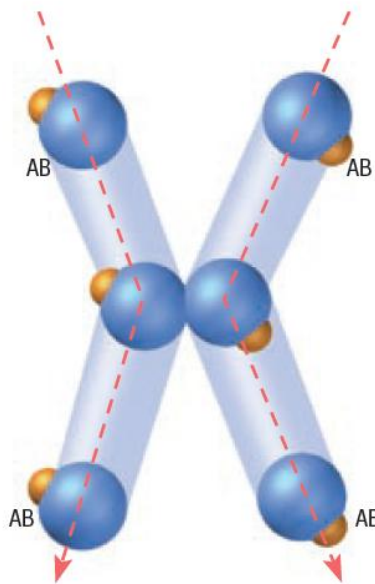
Collision theory



(b) Collision too gentle



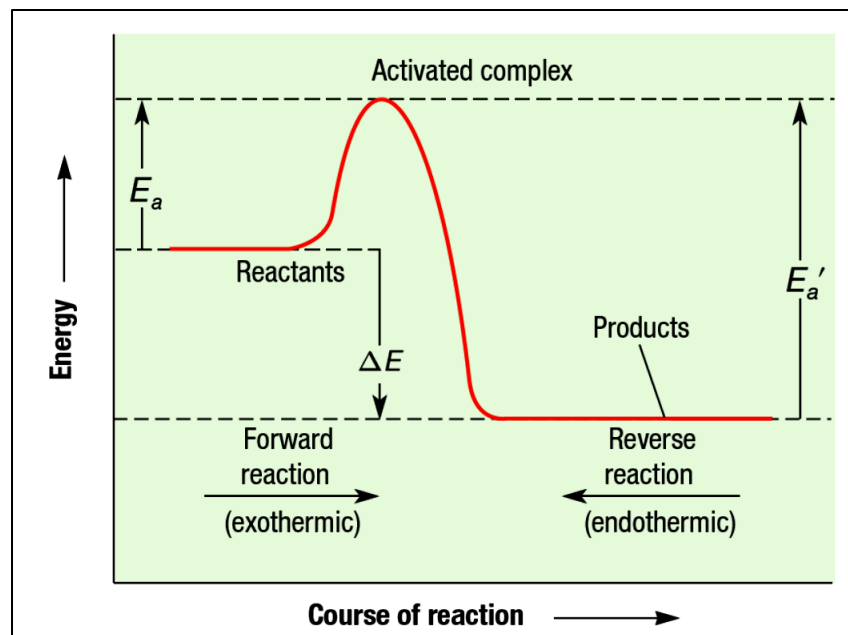
(a) Effective collision, favorable orientation and energy



(c) Collision that has poor orientation

Transition state theory

Transition state (or activated complex) is a combination of molecules which is not a molecule in its own right. The height of the hump corresponds to the activation energy E_a of the reaction.

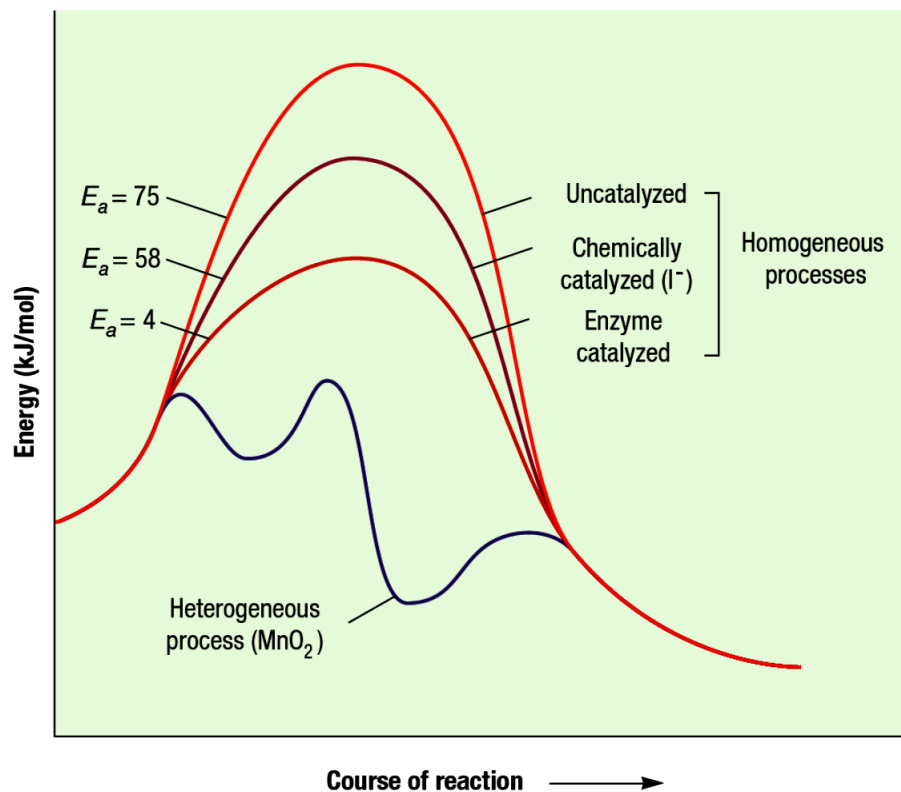


Factor affecting reaction rate.

3. Catalysis effect:

- The rate of a reaction is frequently influenced by the presence of a catalyst.
- A catalyst is defined as a substance that influences the speed of a reaction without itself being altered chemically.
- The catalyst works by changing the mechanism of the reaction and provides a path to the product that has a faster rate-determining step compared to that of the uncatalyzed reaction. another way that catalysts work is by reducing the activation energy of reactions.

Comparison of Pathways for the Decomposition of H_2O_2 by Various Catalysts



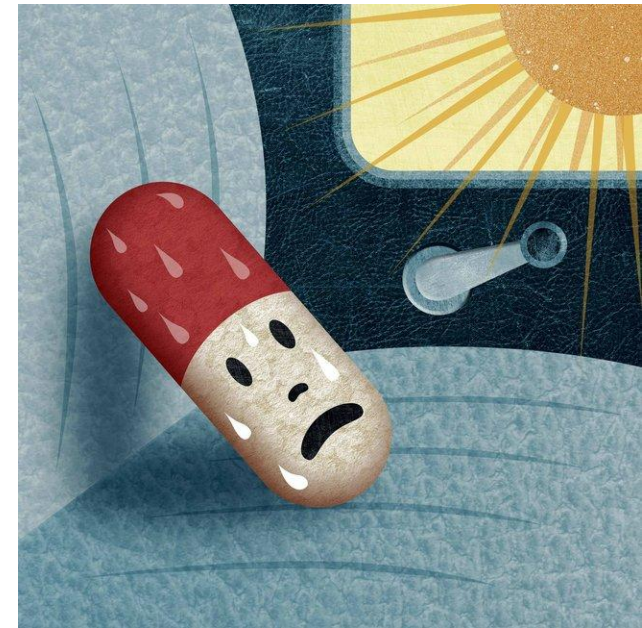
Factor affecting reaction rate.

4. Other factors

- Surface area: Rate of reaction is increased with an increase in surface area
- pH: The rate of reaction is increased by the catalytic effect of hydrogen and hydroxyl ions specific acid base catalysis and by the components of the buffer system general acid base catalysis
- light
- Oxygen

Stability of pharmaceuticals

- Drug stability: The resistance of the drug to the various **chemical, physical, and microbiological reactions** that may change the original properties of the preparations during transport, storage and use and is quantitatively expressed as **shelf life**.
- Knowledge about stability of pharmaceutical substances and dosage forms is very important, and there is a lot of effort to improve stability.
- Pharmaceutical decomposition reactions can be classified as
 - **hydrolysis**
 - **oxidation**
 - **isomerization**
 - **Polymerization**
 - **photolysis**



Questions?

