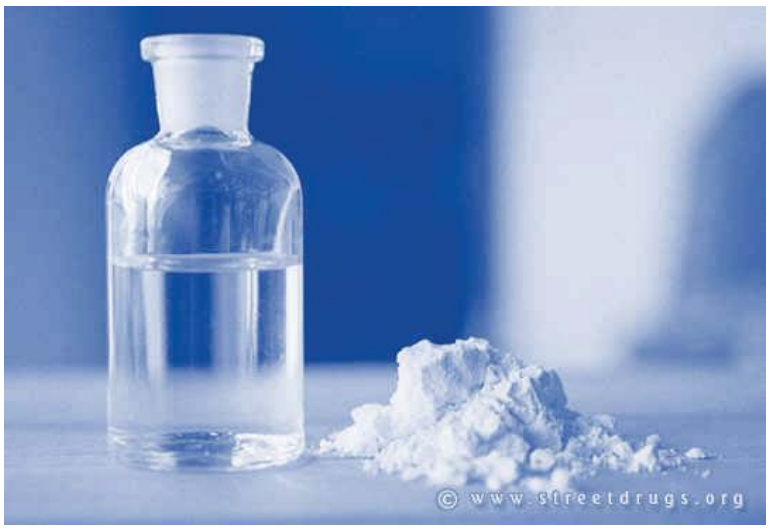
University of Kerbala

Physical Pharmacy

Lecture 3

Chemical Kinetics and Stability



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Overview

Rate and Orders of Reaction

- Rate of Reaction
- Orders of Reaction
- Half-Life and Shelf-Life
- Determination of Reaction Order
- Complex Reactions
- Transition State Theory

Drug Stability

- Drug Decomposition
- Factors influencing Drug stability
- Stability Testing

Learning Objectives

1. Define reaction rate and reaction order.
2. Understand apparent zero-order kinetics and its application.
3. Calculate half-life and shelf life of pharmaceutical products.
4. Understand the basis for transition-state theory and its application to chemical kinetics.
5. Describe the influence of temperature, ionic strength, solvent, pH, and dielectric constant on reaction rates.
6. Calculate the increase in rate constant as a function of temperature.
7. Identify and describe methods for the stabilization of pharmaceutical agents.
8. Understand stability-testing protocols and requirements.

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Rate and Orders of Reaction

Rate of Reaction
Orders of Reaction
Half-Life and Shelf-Life
Determination of Reaction Order
Complex Reactions
Transition State Theory

Rate of Reaction
Rate Law

Chemical Kinetics is the study of chemical reaction rates.

Reaction rate is the change in concentration of a reactant or product over time.

$$\boldsymbol{Reactants \rightarrow Products}$$

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

The relationship between the reactant concentrations and the chemical rate is expressed by a ***Rate law***:

$$\boldsymbol{Rate \propto [A]^x[B]^y}$$

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

Rate is not constant: at any time $\boldsymbol{t}$, it is proportional to concentrations raised to some powers.

Rate of Reaction
Rate Law

Rate constant (k) is a constant that depends only on the temperature (does not depend on concentrations).

K allows to calculate the rate for any concentration.

Exponents $\boldsymbol{x}$ and $\boldsymbol{y}$ are referred to as *reaction order*.

The sum of the exponents of the individual components gives the *overall reaction order*.

E.g.1 $\boldsymbol{A \rightarrow C \quad Rate = k_1[A]^1}$

Overall reaction order = 1 (First order reaction)

E.g.2 $\boldsymbol{A + B \rightarrow C \quad Rate = k_1[A]^1[B]^1}$

Overall reaction order = 1+1 = 2 (Second order reaction)

Based on overall reaction order, 3 types of reaction kinetics are discussed: *zero*, *first*, and *second-order Reactions*.

Orders of Reaction
Zero-Order Reactions

The decomposition proceeds at a constant rate and is independent of the concentrations of any of the reactants.

Examples:

- Photochemical degradation (e.g. chloropromazine)
- Hydrolysis of aqueous drug suspensions.

The rate law is:

$$\boldsymbol{Rate = K_0}$$

Integration of the rate law gives:

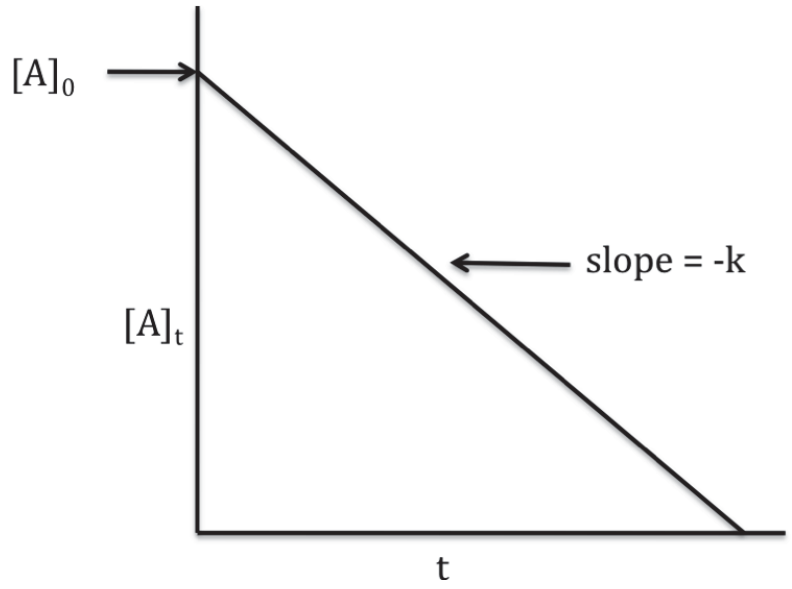
$$\boldsymbol{[A]_t = [A]_0 - K_0 t}$$

$[A]_t$: remaining amount of substance at time t

K_0: zero order rate constant (unit is $concentration.\ time^{-1}$).

Orders of Reaction
Zero-Order Reactions

A plot of $[A]_t$ against t is linear with a slope of K_0 and an intercept of $[A]_0$



Orders of Reaction
First-Order Reactions

The rate depends on the concentration of one reactant.

$$\boldsymbol{A \rightarrow Product}$$

Examples:

- Degradation of aqueous solutions (hydrolysis) of many drugs (e.g. aspirin) and excipients.
- Degradation in some solid or semi-solid dosage forms

The rate equation is:

$$\boldsymbol{Rate = K_1[A]}$$

The integrated rate equation is:

$$\boldsymbol{ln[A]_t = ln[A]_0 - K_1 t}$$

$\boldsymbol{[A]_0}$**:** initial amount of substance

$\boldsymbol{K_1}$: first order rate constant (units are $\boldsymbol{time^{-1}}$).

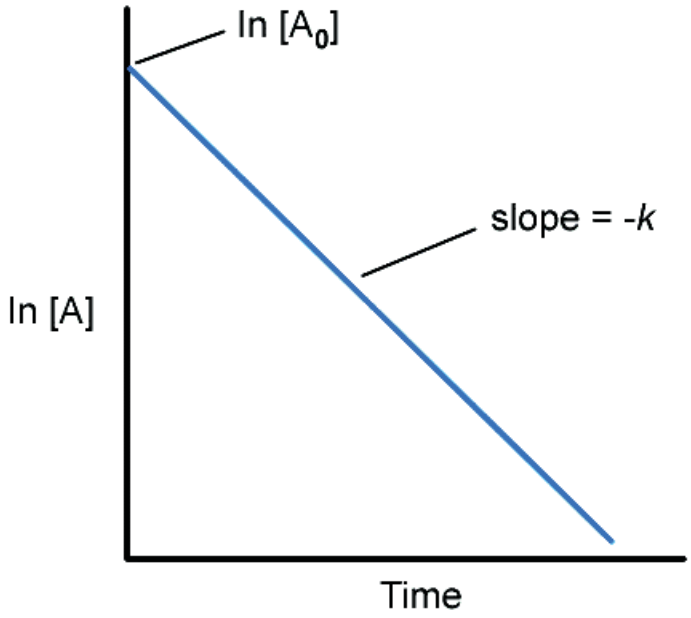
Orders of Reaction
First-Order Reactions
Example

Glucosamine sulfate was found to be most stable at pH of 5 with the degradation constant of $5.39 \times 10^{-6} hr^{-1}$ at 25 °C. Calculate the time taken (in years) for the concentration of the drug to fall to 75% of its original value.

$$\boldsymbol{ln[A]_t = ln[A]_0 - K_1 t}$$
$$ln 0.75 = ln\, 1 - [(5.39 \times 10^{-6})\boldsymbol{t}]$$
$$\boldsymbol{t} = 53373\ hr = 6.09\ year$$

Orders of Reaction
First-Order Reactions

A plot of $\boldsymbol{ln[A]_t}$ against $\boldsymbol{t}$ is linear, with a slope equal to $-\boldsymbol{K_1}$ and an intercept of $\boldsymbol{ln[A]_0}$



Orders of Reaction
First-Order Reactions
Apparent Zero-Order Reactions

Many decomposition reactions in the solid phase or in suspensions "apparently" follow zero-order kinetics.

In case of suspensions, as the drug decomposes in solution, more drug is released from the suspended particles, so that the concentration remains constant.

In case of solutions, the equation is for first-order expression:
$\boldsymbol{Rate = K_1\,[A]}$

In case of suspension the concentration [A] is constant:
$\boldsymbol{K_0 = K_1\,[A]}$

Where $\boldsymbol{K_0}$: pseudo-zero-order rate constant

Thus, $\boldsymbol{Rate = K_0}$

Orders of Reaction
Second-Order Reactions

The rate depends on the concentration of two reacting species, A & B; or two molecules of the same species, 2A:

$\boldsymbol{A + B \rightarrow Product}$ or $\boldsymbol{2A \rightarrow Product}$

For the usual case where the initial concentrations of A and B are different, the rate equation is:

$$\boldsymbol{Rate = K_2[A][B]}$$

The integrated rate equation is:

$$\boldsymbol{ln\frac{[B]_0[A]_t}{[A]_0[B]_t} = K_2t([A]_0 - [B]_0)}$$

Orders of Reaction
Second-Order Reactions

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

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

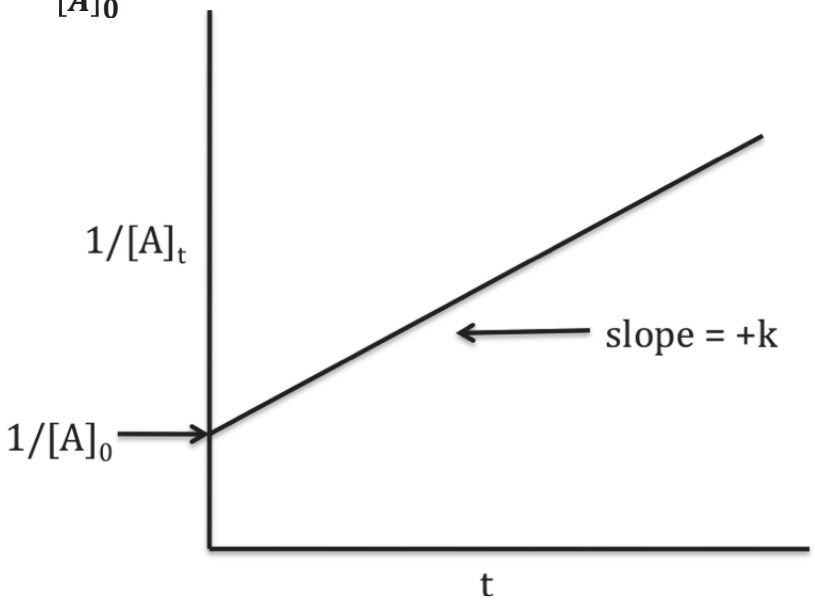
The integrated rate equation is:

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

$\boldsymbol{K_2}$: Second order rate constant (unit is $\boldsymbol{concentration^{-1}time^{-1}}$).

Orders of Reaction
Second-Order Reactions

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



Orders of Reaction
Second-Order Reactions
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.

E.g. $MeAc + H_2O \rightarrow HAc + MeOH$

1M

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

$$Rate = k_2[MeAc][H_2O] = k_1[MeAc]$$

$k_1 = k_2[H_2O]$ is the observed *pseudo first-order rate constant*

This type of reaction is called a *pseudo first-order reaction*.

Half-Life and Shelf-Life

Half-Life ($t_{0.5}$ or $t_{50\%}$) is the time required for one-half of the material to disappear.

The term "half-life" is widely used to express:

- The rate of decay of a radioactive isotope
- The rate at which the drug disappear form the blood (biological half-life).

Shelf-Life ($t_{0.9}$ or $t_{90\%}$) is the time required for 10% of the material to disappear.

The term "shelf-life" is used to express the period of time during which the medicinal product is predicted to remain fit for its intended use under specified conditions of storage.

Half-Life and Shelf-Life
Zero-Order Reaction

The half-life ($t_{50\%}$) of a zero-order reaction is:

$$[A]_t = [A]_0 - K_0 t \qquad \text{At } t = t_{50\%}, [A]_t = 0.5[A]_0$$

$$0.5[A]_0 = [A]_0 - K_0\, t_{50\%}$$

$$t_{50\%} = [A]_0/2K_0$$

The shelf-life ($t_{90\%}$) of a zero-order reaction is:

$$[A]_t = [A]_0 - K_0 t \qquad \text{At } t = t_{90\%}, [A]_t = 0.9[A]_0$$

$$0.9[A]_0 = [A]_0 - K_0\, t_{90\%}$$

$$t_{90\%} = [A]_0/10K_0$$

The half-life and shelf-life are directly proportional with the initial concentration of reactants.

Half-Life and Shelf-Life
Zero-Order Reaction
Example

If aspirin was formulated in a 6.5 g / 100 ml suspension at pH 2.5 and 25ºC where the first-order rate constant is $5 \times 10^{-7} S^{-1}$. It has a solubility of 0.33 g/100 ml. Calculate the half-life of 100 ml of this suspension:

$$\boldsymbol{K_0 = K_1 [A]}$$
$$\boldsymbol{K_0} = (5 \times 10^{-7}) \times 0.33 = 1.65 \times 10^{-7} g/(100\, ml)\, S^{-1}$$

$$\boldsymbol{t_{50\%} = [A]_0 / 2K_0}$$
$$\boldsymbol{t_{50\%}} = \frac{6.5}{2} \times (1.65 \times 10^{-7}) = 1.97 \times 10^{7} S = 228\, days$$

Half-Life and Shelf-Life
First-Order Reaction

The half-life ($\boldsymbol{t_{50\%}}$) of a first-order reaction is:

$$\boldsymbol{ln[A]_t = ln[A]_0 - K_1 t} \quad \Longrightarrow \quad ln0.5[A]_0 = ln[A]_0 - K_0\, t_{50\%}$$

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

The shelf-life ($\boldsymbol{t_{90\%}}$) of a zero-order reaction is:

$$\boldsymbol{ln[A]_t = ln[A]_0 - K_1 t} \quad \Longrightarrow \quad ln0.9[A]_0 = ln[A]_0 - K_0\, t_{90\%}$$

$$\boldsymbol{t_{90\%} = 0.105 / K_1}$$

The half-life and shelf-life are independent of the initial concentration of reactants.

Half-Life and Shelf-Life

First-Order Reaction

Example 1

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?

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

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

Half-Life and Shelf-Life

First-Order Reaction

Example 2

If $[A]_0 = 0.05\ M$ and $k_1 = 2 \times 10^{-2} min^{-1}$, what is the $[A]_t$ after 1 hour and what is the half-life for this reaction?

$$1\ hour = 60\ min$$

$$\boldsymbol{ln[A]_t = ln[A]_0 - K_1 t}$$

$$\boldsymbol{ln[A]_t} = ln\ 0.05 - [(2 \times 10^{-2}) \times 60]$$

$$\boldsymbol{[A]_t} = 6.4 \times 10^{-5} M$$

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

$$\boldsymbol{t_{50\%}} = \frac{0.693}{2 \times 10^{-2}} = 34.65\ min$$

Half-Life and Shelf-Life
Second-Order Reaction

The half-life ($t_{50\%}$) of a second-order reaction is:

$$\frac{1}{[A]_t} = \frac{1}{[A]_0} + K_2 t \quad \Rightarrow \quad \frac{1}{0.5[A]_0} = \frac{1}{[A]_0} + K_2\, t_{50\%}$$

$$t_{50\%} = 1/K_2[A]_0$$

The half-life ($t_{90\%}$) of a second-order reaction is:

$$\frac{1}{[A]_t} = \frac{1}{[A]_0} + K_2 t \quad \Rightarrow \quad \frac{1}{0.9[A]_0} = \frac{1}{[A]_0} + K_2\, t_{90\%}$$

$$t_{90\%} = 0.11/K_2[A]_0$$

The half-life and shelf-life are inversely proportional with the initial concentration of reactants.

Determination of Reaction Order
Substitution Method

The data obtained in a kinetic study is substituted in the integrated laws for the various orders to obtain k values:

Order	Zero	First	Second
Integrated rate law	$[A]_t = [A]_0 - K_0 t$	$ln[A]_t = ln[A]_0 - K_1 t$	$\frac{1}{[A]_t} = \frac{1}{[A]_0} + K_2 t$

The reaction is zero-order if k values calculated from equation: $[A]_t = [A]_0 - K_0 t$ remain constant.

The reaction is 1st-order if k values calculated from equation: $ln[A]_t = ln[A]_0 - K_1 t$ remain constant.

The reaction is 2nd-order if k values calculated from equation: $\frac{1}{[A]_t} = \frac{1}{[A]_0} + K_2 t$ remains constant.

Determination of Reaction Order
Graphic Method

The data obtained in a kinetic study can be plotted according to each reaction order equation until linear plot is obtained.

Order	Zero	First	Second
Graphical plot	$[A]_t$ **vs** t	$ln[A]_t$ **vs** t	$1/[A]_t$ **vs** t

The reaction is zero order if $[A]_t$ vs t gives a straight line.

The reaction is first order if $ln[A]_t$ vs t gives a straight line.

The reaction is second order if $1/[A]_t$ **vs** t gives a straight line.

Determination of Reaction Order
Graphic Method
Example

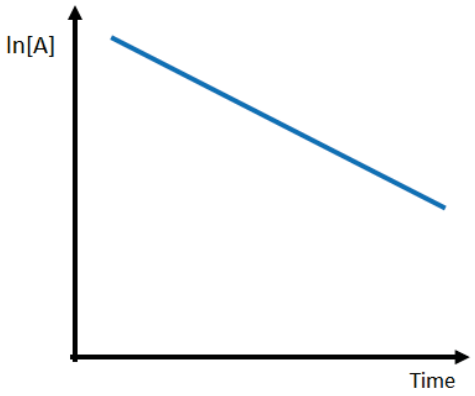
The chemical kinetics of a reaction was investigated. It was found that the initial reactant concentration, which was 0.5 M, reduced to 0.125 M after 180 seconds. Given this information and the graphs provided, determine the rate constant.

The reaction is first order since a plot of ln[A] vs t is linear:

$$ln[A]_t = ln[A]_0 - K_1 t$$

$$ln0.125 = ln0.5 - K_1 \times 180$$

$$K_1 = 7.7 \times 10^{-4} MS^{-1}$$



Determination of Reaction Order

Half-Life Method

The half-lives $t_{50\%}$ for various initial concentrations $[A]_0$ are measured:

Order	Zero	First	Second
Half-life	$t_{50\%} = [A]_0/2K_0$	$t_{50\%} = 0.693/K_1$	$t_{50\%} = 1/K_2[A]_0$

The reaction is zero-order if $t_{50\%}$ increase when $[A]_0$ increase

The reaction is 1st-order if $t_{50\%}$ is not affected by $[A]_0$

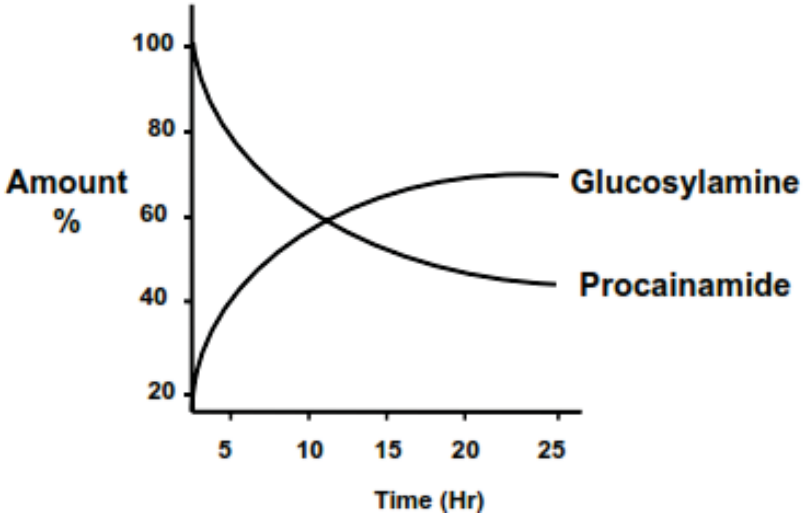
The reaction is 2nd-order if $t_{50\%}$ decrease when $[A]_0$ increase

Complex Reactions

Reversible Reactions

A *reversible* reaction is a reaction that results in an equilibrium mixture of reactants and products

$$A \underset{k_r}{\overset{k_f}{\rightleftharpoons}} B$$



Complex Reactions
Reversible Reactions

The rate law is:

$$\boldsymbol{Rate = k_f[A] - k_r[B]}$$

The integrated rate law:

$$\boldsymbol{ln\frac{[A]_0-[A]_{eq}}{[A]_t-[A]_{eq}} = (k_f + k_r)t}$$

$[A]_{eq}$: the concentration of the reactant at equilibrium

A plot of $\boldsymbol{ln\frac{[A]_0-[A]_{eq}}{[A]_t-[A]_{eq}}}$ against $\boldsymbol{t}$ is linear with a slope of $\boldsymbol{k_f + k_r}$

The equilibrium constant of the reaction is given by:

$$\boldsymbol{K = \frac{k_f}{k_r} = \frac{B_{eq}}{A_{eq}}}$$

Complex Reactions
Reversible Reactions
Example

At pH 4 and 30 °C gave an equilibrium mixture of 37.7% procainamide and 62.3% of the glucosylamine. The plot has a slope of $0.14\ hr^{-1}$. Determine both the forward and reverse rate constants:

$$\boldsymbol{K = \frac{B_{eq}}{A_{eq}}} = \frac{62.3}{37.7} = 1.65 = \boldsymbol{\frac{k_f}{k_r}}$$

$\boldsymbol{Slope = k_f + k_r} = 0.14\ hr^{-1}$ Since $\boldsymbol{k_f} = 1.65\ \boldsymbol{k_r}$

$1.65\ \boldsymbol{k_r} + \boldsymbol{k_r} = 0.14\ hr^{-1}$

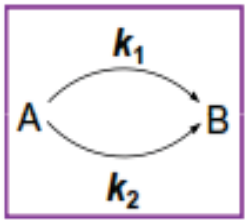
$\boldsymbol{k_r} = 0.156\ hr^{-1}$

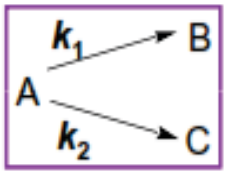
$\boldsymbol{k_f} = 1.65\ \boldsymbol{k_r} = 1.65 \times 0.156 = 0.257\ hr^{-1}$

Complex Reactions

Parallel Reactions

Parallel reaction is a reaction where a reactant either forms a product via two different mechanistic pathways or forms two (or more) different products.





Consecutive Reactions

Consecutive reactions in which drug A decomposes to an intermediate B which then decomposes to product C.

$$A \xrightarrow{k_A} B \xrightarrow{k_B} C$$

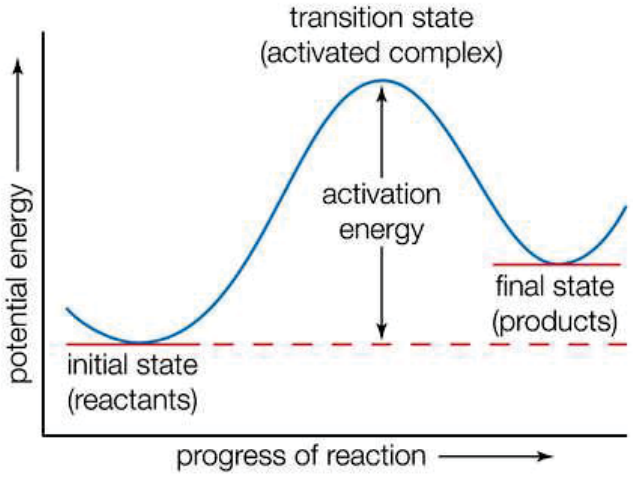
Transition State Theory

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.

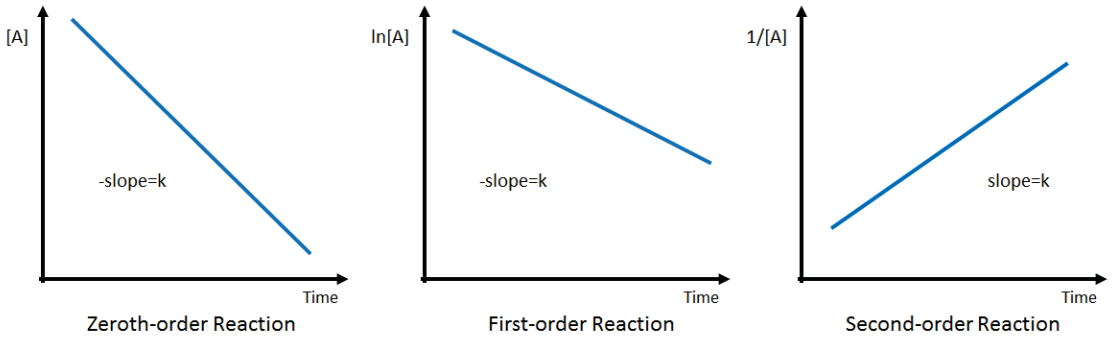
Transition state (or activated complex) is a combination of molecules which is not a molecule in its own right.

The height of the hump corresponds to the activation energy (E_a) of the reaction



Summary

Order	Zero	First	Second
Rate law	$Rate = K_0$	$Rate = K_1[A]$	$Rate = K_2[A]^2$
Rate constant unit	$conc.\, time^{-1}$	$time^{-1}$	$conc.^{-1}\, time^{-1}$
Integrated rate law	$[A]_t = [A]_0 - K_0 t$	$ln[A]_t = ln[A]_0 - K_1 t$	$\frac{1}{[A]_t} = \frac{1}{[A]_0} + K_2 t$
Graphical plot	$[A]_t$ vs t	$ln[A]_t$ vs t	$1/[A]_t$ vs t
Half-life	$t_{50\%} = [A]_0/2K_0$	$t_{50\%} = 0.693/K_1$	$t_{50\%} = 1/K_2[A]_0$
Shelf-life	$t_{90\%} = [A]_0/10K_0$	$t_{90\%} = 0.105/K_1$	$t_{90\%} = 0.11/K_2[A]_0$



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Drug Stability

Drug Decomposition
Factors influencing Drug stability
Stability Testing

Drug Decomposition

Drugs may break down in solution and also in the solid state (for example, in tablet or powder form).

It is often possible to predict which drugs are likely to decompose by looking for specific chemical groups in their structures.

The main ways in which drugs break down are as follows:

1. **Hydrolysis** (very common)
2. **Oxidation** (very common)
3. **Isomerization**
4. **photochemical decomposition**
5. **polymerization of drugs**

Drug Decomposition
Hydrolysis

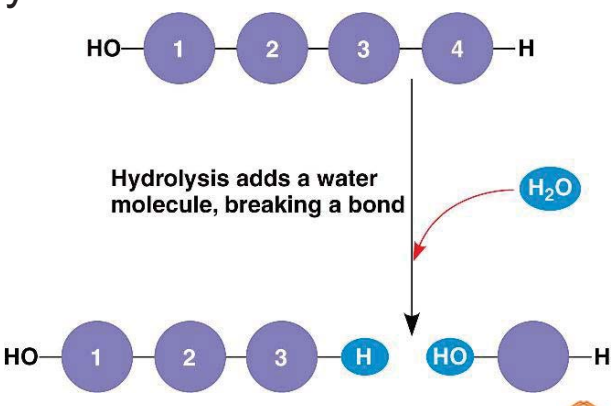
Hydrolysis means the cleavage of chemical bonds by the addition of water.

Hydrolysis can be catalysed by hydrogen ions (specific acid catalysis) or hydroxyl ions (specific base catalysis).

Drugs containing ester, amide, lactam, imide or carbamate groups are susceptible to hydrolysis.

Solutions can be stabilised by:

- formulating at the pH of maximum stability.
- Altering the dielectric constant by the addition of non-aqueous solvents.



Drug Decomposition
Oxidation

Oxidation involves the removal of an electropositive atom (e.g. hydrogen) or electron, or the addition of an electronegative atom (e.g. oxygen).

Drugs that are susceptible to oxidation include steroids, polyunsaturated fatty acids, and drugs that contain conjugated double bonds.

Formulations can be stabilized by:

- Replacing the oxygen in pharmaceutical containers with nitrogen or carbon dioxide.
- Avoiding contact of the drug with heavy-metal ions such as iron, cobalt or nickel (they catalyze oxidation)
- Antioxidants should be included in the formulation.

Drug Decomposition
Isomerization

Isomerization is the process of conversion of a drug (e.g. adrenaline) into its optical or geometric isomers, which are often of lower therapeutic activity.

Photochemical Decomposition

Light energy, like heat, may provide the activation necessary for the degradation of some drugs (e.g. phenothiazines)

Polymerization

Polymerization is the process by which two or more identical drug molecules (e.g. ampicillin) combine together to form a complex molecule.

Factors Influencing Drug Stability
Temperature

Increase in temperature usually causes a very pronounced increase in the hydrolysis rate of drugs in solution.

The equation which describes the effect of temperature on decomposition is the *Arrhenius equation*:

$$\boldsymbol{lnk = lnA - E_a/RT}$$

$\boldsymbol{k}$: rate constant

$\boldsymbol{E_a}$: activation energy (J mol^{-1})

$\boldsymbol{A}$: the Arrhenius constant

$\boldsymbol{R}$: gas constant (8.314 J mol^{-1} K^{-1})

$\boldsymbol{T}$: temperature (kelvins).

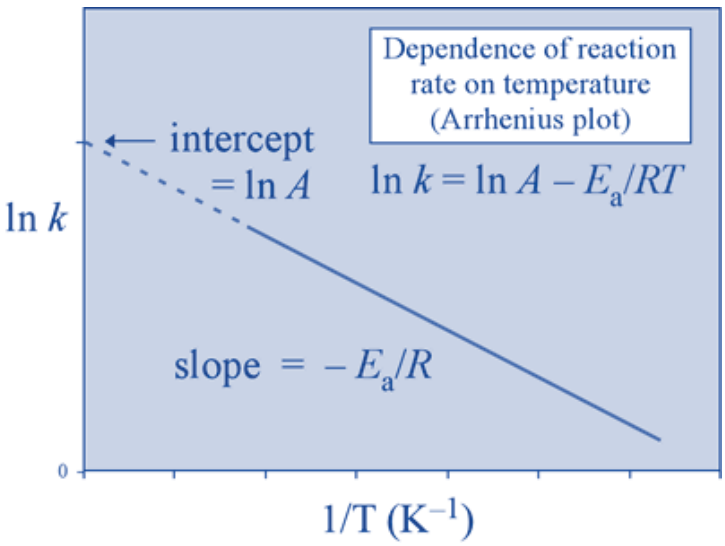
Rate constants are temperature dependent

Factors Influencing Drug Stability
Temperature

Plot of $\boldsymbol{lnk}$ against $\boldsymbol{1/T}$ is linear with a slope of $\boldsymbol{-E_a/R}$ and an intercept of $\boldsymbol{lnA}$

Arrhenius plot is used to theoretically estimate the rate constant at room temperature (where reaction occurs at a rate too slow to measure)

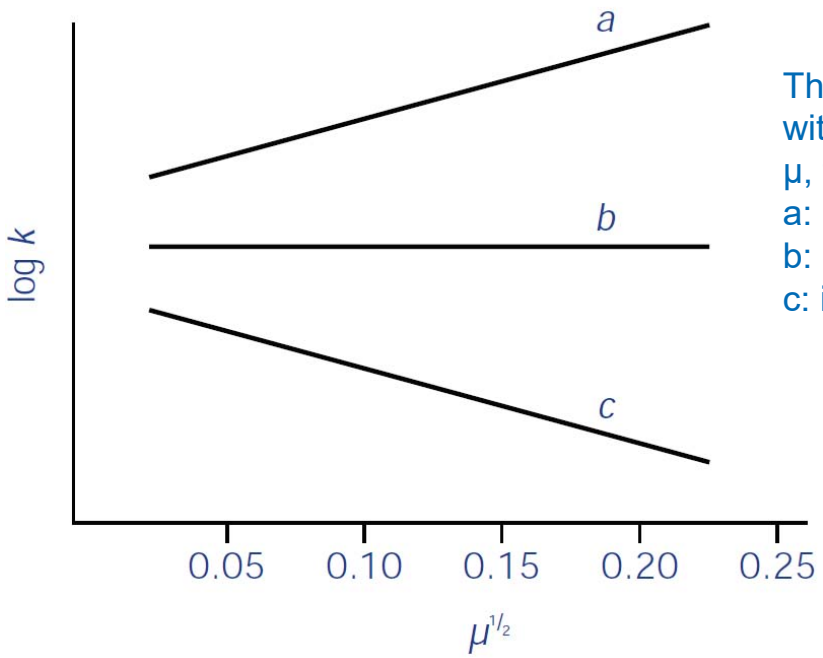
This method speeds up the measurements of drug stability during pre-formulation



Factors Influencing Drug Stability
Ionic Strength

a. If the reactants share the same charge, the activated complex will be more highly charged than the reactants. Increasing the ionic strength of the solution will therefore have a greater stabilizing effect upon the complex than on the reactants, and will thus increase the rate constant by lowering the activation energy.
b. If the reactants are oppositely charged, the charge on the activated complex will be lower than the charges on the reactants, and the rate constant will decrease with ionic strength.
c. If one of the reactants is uncharged, there will be no change in the rate constant with ionic strength.

Factors Influencing Drug Stability
Ionic Strength

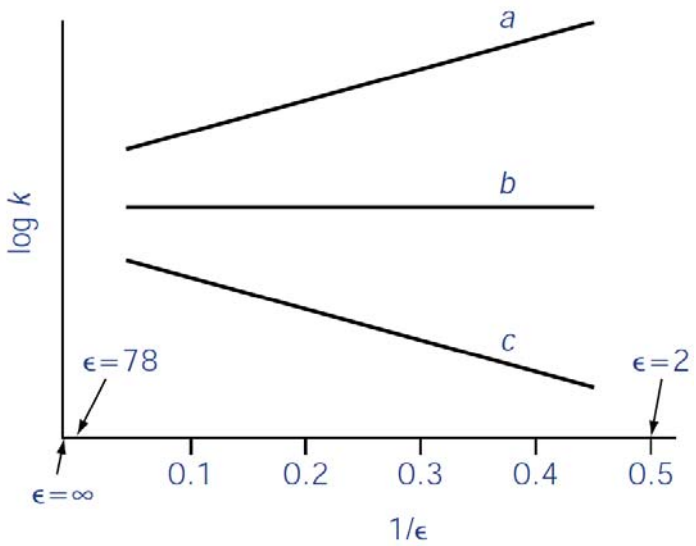


The variation of rate constant, *k*, with square root of ionic strength, μ, for reaction between:
a: ions of similar charge,
b: ion and uncharged molecule and
c: ions of opposite charge.

Factors Influencing Drug Stability
Solvent Effect

For ions of like charge, an increase in dielectric constant of the solvent results in an increase in the rate of the reaction.

For a reaction between ions of opposite sign, an increase in dielectric constant results in a decrease in the rate constant.



The variation of rate constant with reciprocal of dielectric constant for reaction between:
a: ions of opposite charge,
b: ion and uncharged molecule
C: ions of similar charge

Factors Influencing Drug Stability
Catalyst

Catalyst is a substance that increases the speed of a reaction without itself being altered chemically, by lowering the activation energy.

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*).

Other Factors

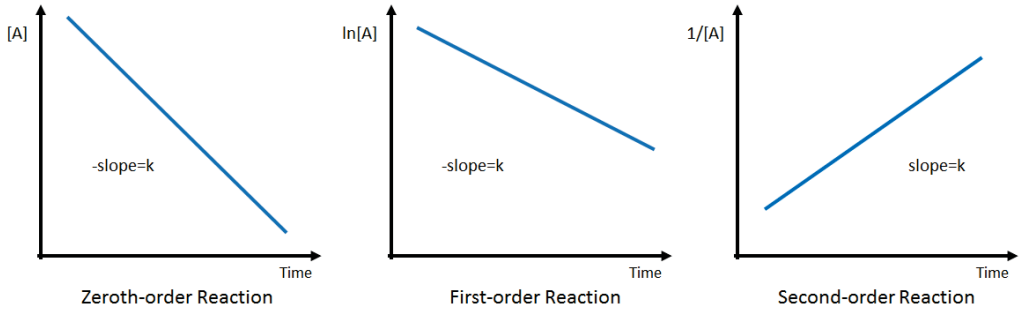
- **Particle size:** Rate of reaction is increased with and increase in surface area
- **Light**
- **Oxygen**

Stability Testing

The Arrhenius equation is used for accelerating decomposition by raising the temperature of the preparations to rapidly identify the most suitable one during preformulation.

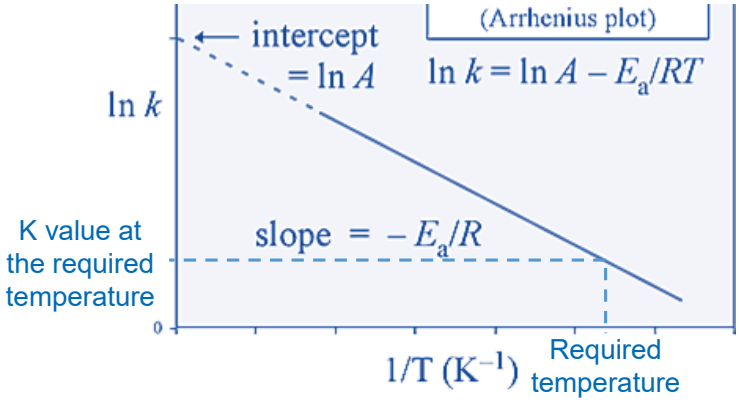
The main steps in the process are:

1. Reaction order is determined graphically by plotting stability data vs time according to each reaction order equation until linear plot is obtained.



Stability Testing

2. The rate constant $\boldsymbol{k}$ is calculated at several elevated temperature from the slope of these plots and $\boldsymbol{lnk}$ is plotted against $\boldsymbol{1/T}$ according to Arrhenius equation:
$\boldsymbol{lnk = lnA - E_a/RT}$



3. A value of $\boldsymbol{k}$ can be interpolated from this plot at the required temperature.
4. The shelf-life for the product can be calculated from the rate constant at the required temperature.

Stability Testing

Alternatively, if only an approximate value of $\boldsymbol{k}$ is required at temperature $\boldsymbol{T_1}$, then this may be estimated from measurements at a single higher temperature $\boldsymbol{T_1}$ using:

$$\boldsymbol{ln\frac{k_2}{k_1} = -\frac{E_a}{R}\left(\frac{1}{T_2} - \frac{1}{T_1}\right)}$$

$\boldsymbol{k_1}$ & $\boldsymbol{k_2}$ = rate constants at $\boldsymbol{T_1}$ and $\boldsymbol{T_2}$ respecitvely

$\boldsymbol{E_a}$ = activation energy (J mol^{-1})

$\boldsymbol{R}$ = gas constant (8.314 J mol^{-1} K^{-1})

$\boldsymbol{T_1}$ & $\boldsymbol{T_2}$ = required temperature and high temperature respectively (kelvins)

Stability Testing
Example

Given the following data, determine the activation energy for the chemical reaction.

Temperature (°C)	Rate Constant ($M^{-1}\,S^{-1}$)
30	0.34
60	0.80

$$\boldsymbol{ln\frac{k_2}{k_1} = -\frac{E_a}{R}\left(\frac{1}{T_2} - \frac{1}{T_1}\right)}$$

$$ln\frac{0.80}{0.34} = -\frac{E_a}{8.314}\left(\frac{1}{333} - \frac{1}{303}\right)$$

$$E_a = 23927\frac{\text{J}}{\text{mol}} = 23.927\frac{\text{KJ}}{\text{mol}}$$

References

Attwood, D. & Florence, A. T. 2008. *Physical pharmacy,* London. Chicago, Pharmaceutical Press.

Sinko, P. J. M. a. N. 2006. *Martin's physical pharmacy and pharmaceutical sciences: physical chemical and biopharmaceutical principles in the pharmaceutical sciences,* Philadelphia, Lippincott Williams & Wilkins.