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**UNIVERSITY OF BASRAH**

# Chemical Kinetics & Stability

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2017/2018

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# Outlines

➢Kinetics

➢Rate and orders of reactions,

➢Influence of temperature and other factors on reactions rate.

➢Decomposition of medicinal agents and accelerated stability analysis.

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# Is it important to study Kinetics?

- Kinetics and stability show how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as **temperature**, **humidity**, and **light.**

- They help to establish a retest period for the drug substance or a shelf life and specify storage conditions.

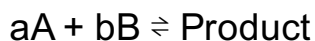- Finding solutions for instability problems.

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# Rate & order of reaction

**Rate**: The velocity with which a reaction or a process occurs.

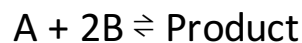**Order**: The influence of concentration of drugs on the rate of reaction

$$aA + bB \rightleftharpoons Product$$

Rate = $dc/dt \propto [A]^a[B]^b = K [A]^a[B]^b$

If B is a solvent ……
**Pseudo-first order** is ……

Example:

$A + 2B \rightleftharpoons Product$

$K [A] [B]^2$

Order of A = **1**

Order of B = **2**

Total Order = **3**

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$$CH_3COOC_2H_5 + NaOH_{soln} \rightarrow CH_3COONa + C_2H_5OH$$

$$\text{Rate} = k[CH_3COOC_2H_5]^1 [NaOH]^1$$

The reaction is first order ($a = 1$) with respect to ethyl acetate and first order ($b = 1$) with respect to sodium hydroxide solution; overall the reaction is second order ($a + b = 2$).

## NaOH Solution = Access

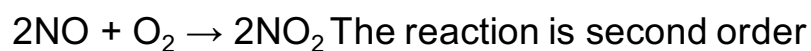$$\text{Rate} = \frac{d[CH_3COOC_2H_5]}{dt} = k'[CH_3COOC_2H_5] \quad \text{Ethyl acetate dependent}$$

## Therefore: Reaction is pseudo 1$^{st}$ Order

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# Molecularity

• The rate limiting step of a chemical process is ……..

• Example:

$$2NO + O_2 \rightarrow 2NO_2 \quad \text{The reaction is second order}$$
$$2NO \rightarrow N_2O_2 \quad \text{Slowest step}$$
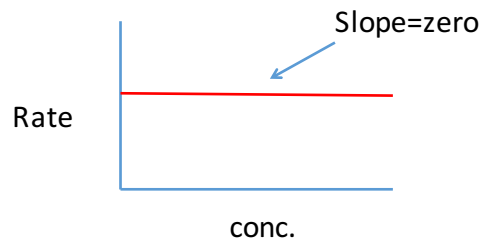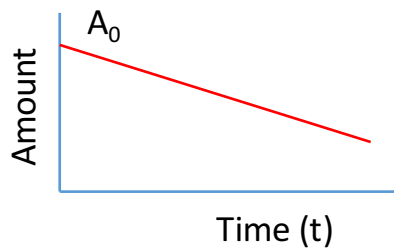$$N_2O_2 + O_2 \rightarrow 2NO$$



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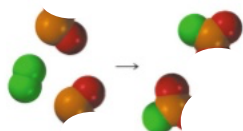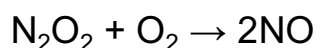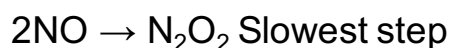
## Rate constant ?  = K depends on …..

### Unite of rate constant ? Depends on the order of reaction

## Zero Order??? Example
### Independent on the Conc

$A_0$

Amount

Time (t)

Slope=zero
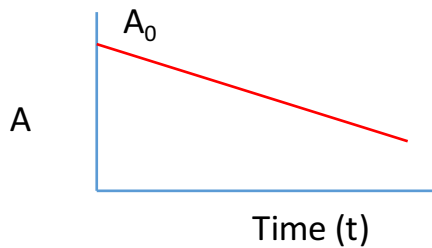
Rate

conc.

---

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

$$\int_{A_0}^{A_t} dA = -k_0 \int_0^t dt$$

$$A_t - A_0 = -k_0 t$$

$$A_t = A_0 - k_0 t$$

$A_0$

A

Time (t)

$$k = -\frac{dA}{dt} = \frac{moles/liter}{second}$$
$$= moles\ liter^{-1}\ second^{-1}$$

$A_0$

$A$

$\frac{1}{2}A$

$t_{1/2}$  Time (t)
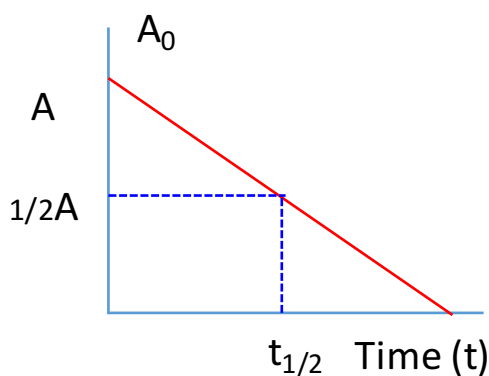
$$A_t = A_0 - k_0 t$$

$$0.5A_0 = A_0 - k_0 t_{0.5}$$

$$t_{0.5} = \frac{A_0 - 0.5A_0}{k_0} = \frac{0.5A_0}{k_0}$$

- ➤ Shelf life is ……
- ➤ For zero order kinetic it can be calculated ……….

| Time (m) | Amount (Moles/Liter) |
|----------|----------------------|
| 0 | 100 |
| 10 | 80 |
| 20 | 59 |
| 30 | 41 |
| 40 | 20 |
| 50 | 2 |

$$A_t = A_0 - k_0 t$$

$$Rate = k_0 = \frac{dA}{dt} = \frac{20}{10} = 2\,mole.liter^{-1}.\min utes^{-1}$$

$$Half - life = t_{0.5} = \frac{0.5A_0}{k_0} = \frac{50}{2} = 25\,\min utes$$

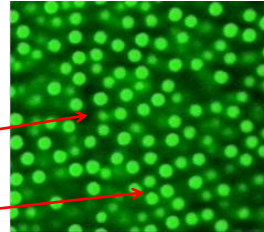$$t_{0.9} = \frac{0.1A_0}{k_0} = \frac{10}{2} = 5\,\min utes$$
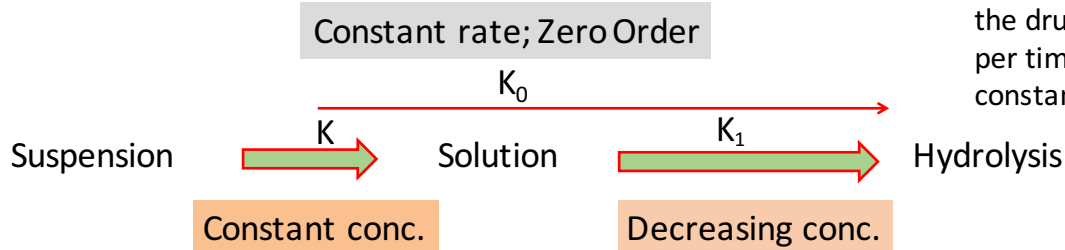
# Suspension, Apparent Zero-Order Kinetics

Hydrolysis of drug should be in solution??

There are two concentrations of drug in suspension

1-Solution (saturation)

2-Suspension of insoluble solids

Excess solid will act as a reservoir for solid so that the concentration will not change significantly and so the amount of the drug degraded per time will be constant

Constant rate; Zero Order

$K_0$

Suspension →$K$→ Solution →$K_1$→ Hydrolysis

Constant conc.           Decreasing conc.

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**EXAMPLE 14–2**

**Shelf Life of an Aspirin Suspension**

A prescription for a liquid aspirin preparation is called for. It is to contain 325 mg/5 mL or 6.5 g/100 mL. The solubility of aspirin at 25°C is 0.33 g/100 mL; therefore, the preparation will definitely be a suspension. The other ingredients in the prescription cause the product to have a pH of 6.0. The first-order rate constant for aspirin degradation in this solution is $4.5 \times 10^{-6}$ sec$^{-1}$. Calculate the zero-order rate constant. Determine the shelf life, $t_{90}$, for the liquid prescription, assuming that the product is satisfactory until the time at which it has decomposed to 90% of its original concentration (i.e., 10% decomposition) at 25°C.

$K_0$= Solubility . k

*Answer:* $k_0 = k \times$ [Aspirin in solution], from equation (14–9).

Thus,

$$k_0 = (4.5 \times 10^{-6} \text{ sec}^{-1}) \times (0.33 \text{ g}/100 \text{ mL})$$

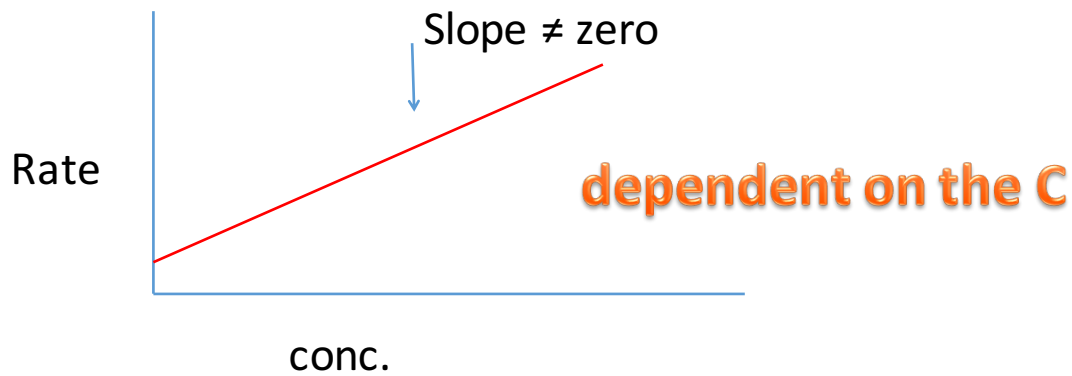$$k_0 = 1.5 \times 10^{-6} \text{ g}/100 \text{ mL sec}^{-1}$$

$$t_{90} = \frac{0.10[A]_0}{k_0} = \frac{(0.10)(6.5 \text{ g}/100 \text{ mL})}{(1.5 \times 10^{-6} \text{ g}/100 \text{ mL sec}^{-1})}$$

$$= 4.3 \times 10^5 \text{ sec} = 5.0 \text{ days}$$

# First Order??? Example

Slope ≠ zero

Rate

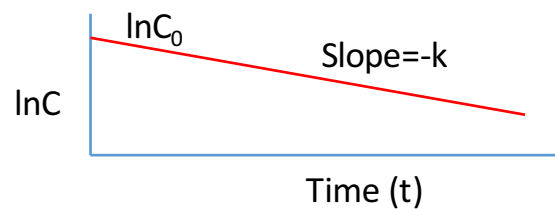**dependent on the C**

conc.

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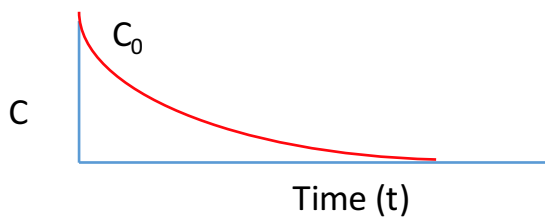
$$-\frac{dc}{dt} = kc$$

$$\int_{c_0}^{c} \frac{dc}{c} = -k \int_{0}^{t} dt$$

$$\ln c - \ln c_0 = -k(t - 0)$$

$$\ln c = \ln c_0 - kt$$

$C_0$

$C$

InC$_0$

Slope=-k

InC

Time (t)

Time (t)

$$-\frac{dc}{dt} = kc \implies k = -\frac{dc}{dt}\frac{1}{c} = \frac{\text{moles/liter}}{\text{second-moles/liter}}$$

$$= \frac{1}{\text{second}} = \text{second}^{-1}$$

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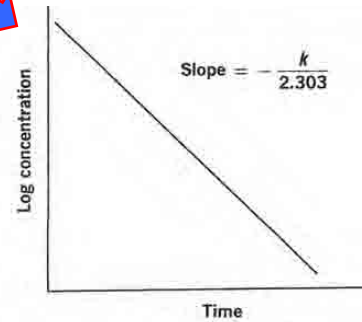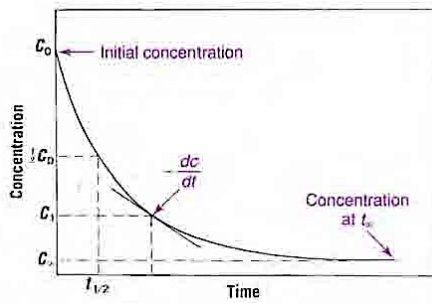
$$\ln c = \ln c_0 - kt \qquad\qquad c = c_0 e^{-kt}$$

$$\log c = \log c_0 - kt/2.303 \qquad c = c_0 10^{-kt/2.303}$$

$$k = \frac{2.303}{t} \log \frac{c_0}{c} \qquad\qquad k = \frac{2.303}{t} \log \frac{a}{a-x}$$

$$Half-life = t_{0.5} = \frac{2.303}{k} . \log \frac{2}{1}$$

$$= \frac{2.303 \times 0.3}{k}$$

$$= \frac{0.693}{k} \, minutes$$

$$Shelf-life = t_{0.9} = \frac{2.303}{k} . \log \frac{10}{9}$$

$$= \frac{2.303 \times 0.045}{k} = \frac{0.105}{k} \, minutes$$

**TABLE 14–1**

**DECOMPOSITION OF HYDROGEN PEROXIDE AT 25°C IN AQUEOUS SOLUTION CONTAINING 0.02 M KI***

| $t$ (min) | $a - x$ | $K$ (min$^{-1}$) |
|---|---|---|
| 0 | 57.90 | — |
| 5 | 50.40 | 0.0278 |
| 10 | 43.90 | 0.0277 |
| 25 | 29.10 | 0.0275 |
| 45 | 16.70 | 0.0276 |
| 65 | 9.60 | 0.0276 |
| ∞ | 0 | — |

K was Calculated using $\qquad$ $k = \frac{2.303}{t} \log \frac{c_0}{c}$

## EXAMPLE 14-3

**Decomposition of Hydrogen Peroxide**

The catalytic decomposition of hydrogen peroxide can be followed by measuring the volume of oxygen liberated in a gas burette. From such an experiment, it was found that the concentration of hydrogen peroxide remaining after 65 min, expressed as the volume in milliliters of gas evolved, was 9.60 from an initial concentration of 57.90.

(a) Calculate $k$ using equation (14–14).
(b) How much hydrogen peroxide remained undecomposed after 25 min?

(a)
$$k = \frac{2.303}{65} \log \frac{57.90}{9.60} = 0.0277 \, \text{min}^{-1}$$

(b)
$$0.0277 = \frac{2.303}{25} \log \frac{57.90}{c}; c = 29.01$$

## EXAMPLE 14-4

**First-Order Half-Life**

A solution of a drug contained 500 units/mL when prepared. It was analyzed after 40 days and was found to contain 300 units/mL. Assuming the decomposition is first order, at what time will the drug have decomposed to one-half of its original concentration?

We have

$$k = \frac{2.303}{40} \log \frac{500}{300} = 0.0128 \, \text{day}^{-1}$$

$$t = \frac{2.303}{0.0128} \log \frac{500}{250} = 54.3 \, \text{days}$$

# True or False

- In **First order kinetics** each of the following parameters **depend on Concentration**:
  a) Rate
  b) Rate constant
  c) Half life
  d) Shelf life

- In **Zero order kinetics** each of the following parameters **depend on Concentration**:
  a) Rate
  b) Rate constant
  c) Half life
  d) Shelf life

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**2ⁿᵈ order reactions:** the rate of bimolecular rx which occur when 2 molecules come togethe
1-Speed of reaction depends on the concentration of both reactants.
2-The rate of decomposition of A is equal to rate of decomposition of B and both are proportional to product concentration.

$$A + B \rightarrow \text{Products}$$
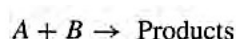
$$\text{Rate} = -\frac{d[A]}{dt} = \frac{d[B]}{dt} = k[A][B]$$

Where a and b are the initial conc. of A and B

$$\text{Rate} = \frac{dx}{dt} = k(a-x)(b-x)$$

Amount remaining

$$k = \frac{2.303}{t(a-b)} \log \frac{b(a-x)}{a(b-x)}$$

Where:
a: Initial concentration of [A]
b: Initial concentration of [B]
x : reacting concentration at time t

When a=b
$$\frac{dx}{dt} = k(a-x)^2 = kC^2$$

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$$\int_0^x \frac{dx}{(a-x)^2} = k\int_0^t dt \quad \Longrightarrow \quad \left(\frac{1}{a-x}\right) - \left(\frac{1}{a-0}\right) = kt$$

$$\frac{x}{a(a-x)} = kt \quad \Longrightarrow \quad k = \frac{1}{at}\left(\frac{x}{a-x}\right)$$

Law of 2$^{nd}$ order

$$t_{0.5} = \frac{1}{ak} \qquad \frac{x}{a(a-x)} = kt$$

**Only when a=b**

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**EXAMPLE 14–5**

**Saponification of Ethyl Acetate**

Walker[6] investigated the saponification of ethyl acetate at 25°C:

$$CH_3COOC_2H_5 + NaOH \rightarrow CH_3COONa + C_2H_5OH$$

The initial concentrations of both ethyl acetate and sodium hydroxide in the mixture were 0.01000 M. The change in concentration, $x$, of alkali during 20 min was 0.000566 mole/liter; therefore, $(a - x) = 0.01000 - 0.00566 = 0.00434$.

Compute (a) the rate constant and (b) the half-life of the reaction.

(a) Using equation (14–23), we obtain

$$k = \frac{1}{0.01 \times 20} \frac{0.00566}{0.00434} = 6.52 \text{ liter mole}^{-1} \text{ min}^{-1}$$
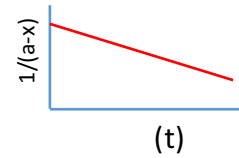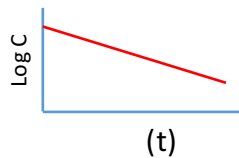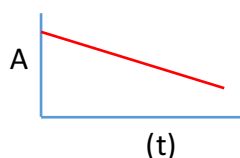
(b) The half-life of a second-order reaction is

$$t_{1/2} = \frac{1}{ak} \qquad\qquad (14\text{–}26)$$

# Determination of order

1) Substitution method: using rate order equations and check k if constant indicates that order.

2) Graphical method (applied data to get straight line)



3) Half life method

**Table 14–2.** The half-life of a first-order reaction is independent of $a$; $t_{1/2}$ for a second-order reaction, in which $a = b$, is proportional to $1/a$; and in a third-order reaction, in which $a = b = c$, it is proportional to $1/a^2$. The relation-

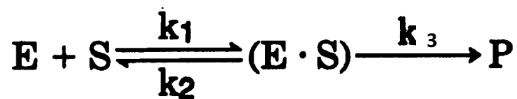$$t_{0.5} \propto \frac{1}{a^{n-1}}$$

# Determination of order

**TABLE 14–2**
**RATE AND HALF-LIFE EQUATIONS**

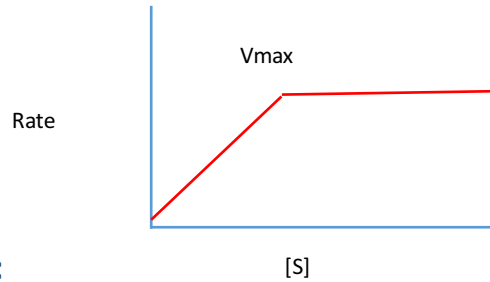| Order | Integrated Rate Equation | Half-Life Equation |
|-------|--------------------------|--------------------|
| 0 | $x = kt$ | $t_{1/2} = \dfrac{a}{2k}$ =0.5A/k |
| 1 | $\log \dfrac{a}{a-x} = \dfrac{k}{2.303}t$ | $t_{1/2} = \dfrac{0.693}{k}$ |
| 2 | $\dfrac{x}{a(a-x)} = kt$ | $t_{1/2} = \dfrac{1}{ak}$ |
| 3 | $\dfrac{2ax - x^2}{a^2(a-x)^2} = 2kt$ | $t_{1/2} = \dfrac{3}{2}\dfrac{1}{a^2k}$ |

# Michaelis –Menten Equation

- Saturated kinetics:

$$E + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} (E \cdot S) \overset{k_3}{\longrightarrow} P$$

$$V = V_m \frac{S}{k_m + S}$$

Rate

Vmax

[S]

**Where:**
**S = substrate**
**Vm = maximum velocity**
**V = velocity**
**Km = M-M constant**

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# Michaelis – Menten Equation

- Saturated kinetics:
- Straight line equation:

$$Y = b + a (X)$$

$$\Updownarrow \quad \Updownarrow \quad \Updownarrow \quad \Updownarrow$$

$$\frac{1}{V} = \frac{1}{V_m} + \frac{K_m}{V_m}\frac{1}{S}$$

$\frac{1}{V}$

Intercept
$1/V_m$

Slope
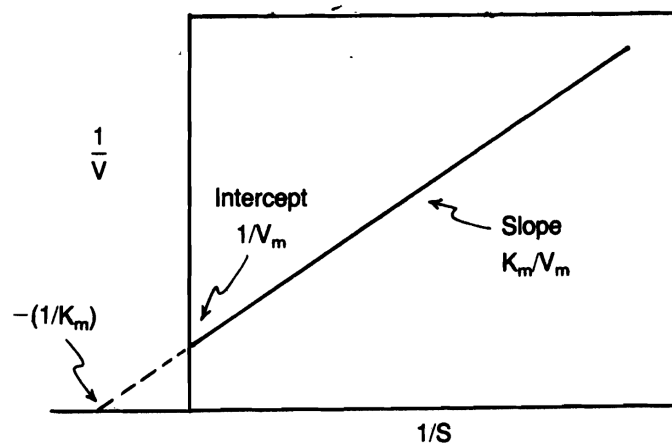$K_m/V_m$

$-(1/K_m)$

$1/S$

**Fig. 12–5.** A Lineweaver–Burk plot of Michaelis–Menten kinetics

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# Factors influencing reaction

Temperature

Solvent effect

Ionic strength
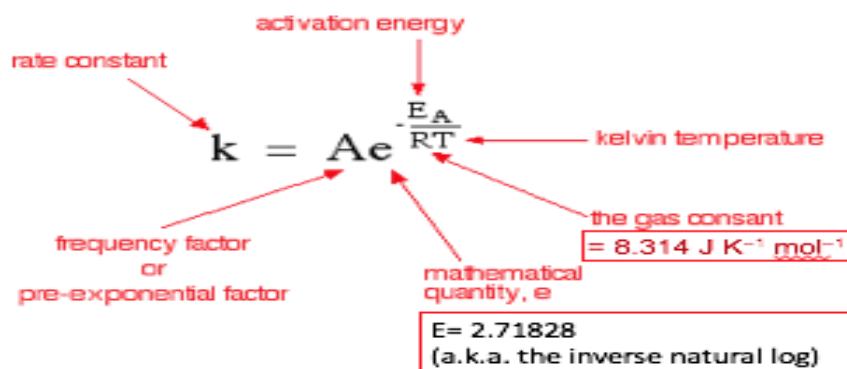
pH

Oxygen

Light

## 1) Temperature effect

### Collision theory:

- Rate depends on number of molecular collision per time

- Heat increases collision and so --------- rate constant.

- Around 10ºC increased result in double or triple K.

- Activation Energy: Ea …….

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# The Arrhenius equation

rate constant

activation energy

$$k = Ae^{-\frac{E_A}{RT}}$$

kelvin temperature

frequency factor
or
pre-exponential factor

mathematical
quantity, e

the gas consant
= 8.314 J K⁻¹ mol⁻¹

E= 2.71828
(a.k.a. the inverse natural log)

- $^0C + 273 = K$

**The Arrhenius equation is used to describe, mathematically, the exponential relationship between the rate constant and the temperature.**

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## Arrhenius equation

$$k = Ae^{-E/RT}$$

$$\log k = \log A - \frac{E_a}{2.303} \cdot \frac{1}{RT}$$
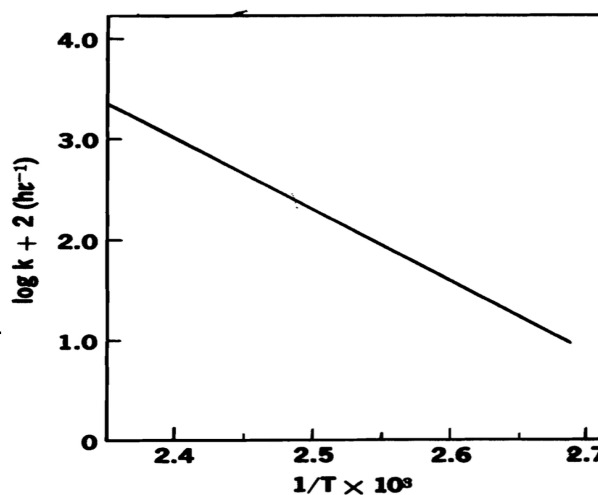
$t_{0.5}$ and 1/T correlation is .......

Fig. 12−6. A plot of log $k$ against 1/$T$ for the thermal decompos of glucose.

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# Arrhenius equation

- At two temperature the equation will be:

$$\log \frac{k_2}{k_1} = \frac{E_a}{2.303R}\left(\frac{T_2 - T_1}{T_2 T_1}\right)$$

- $Q_{10}$ is : ......

$$Q_{10} = \frac{k_{(T+10)}}{k_T} \qquad Q_{10} = \exp\left[-\frac{E_a}{R}\left(\frac{1}{T+10} - \frac{1}{T}\right)\right]$$

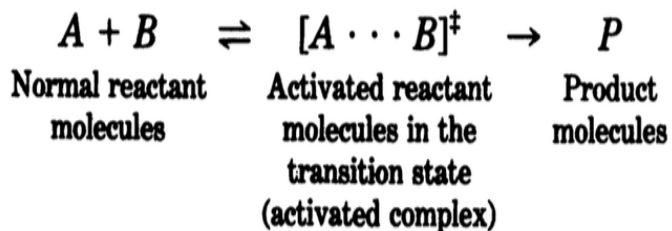- Ea ranges from 12-24 Kcal/mole so $Q_{10}$ will be 2-4 when Temperature increased from 20º to 30º, How?

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# Temperature effect

**Transition-State theory:**

The formation of Activated complex,

$$A + B \ \rightleftharpoons\ [A \cdots B]^{\ddagger} \ \rightarrow\ P$$

Normal reactant molecules

Activated reactant molecules in the transition state (activated complex)

Product molecules

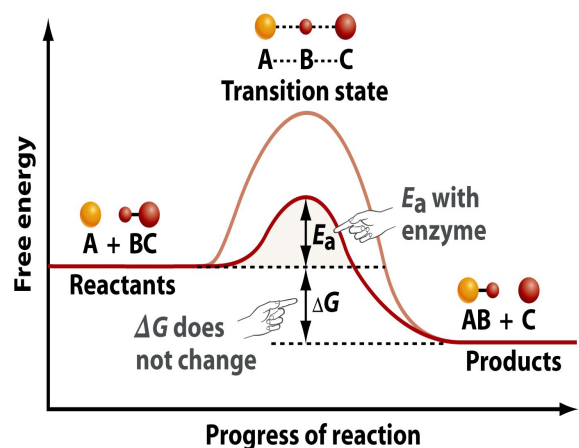The Ea according to this theory is ........



Figure 3-21 Biological Science, 2/e        © 2005 Pearson Prentice Hall, Inc.

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# Accelerated Stability analysis or Stress testing

➢Regulatory required both **full and long term study** and and **accelerated study** to determine the shelf life.

➢Any change in the manufacture steps (even the packaging material) required new stability study.

➢Accelerated study: design to increase the rate of degradation by using exaggerated conditions of temp and humidity

| Climatic zone | Definition | Criteria<br>Mean annual temperature measured in the open air/ mean annual partial water vapour pressure | Long-term testing conditions |
|---|---|---|---|
| I | Temperate climate | ≤ 15 °C / ≤ 11 hPa | 21 °C / 45% RH |
| II | Subtropical and Mediterranean climate | > 15 to 22 °C / > 11 to 18 hPa | 25 °C / 60% RH |
| III | Hot and dry climate | > 22 °C / ≤ 15 hPa | 30 °C / 35% RH |
| IVA | Hot and humid climate | > 22 °C / > 15 to 27 hPa | 30 °C / 65% RH |
| IVB | Hot and very humid climate | > 22 °C / > 27 hPa | 30 °C / 75% RH |

# Steps of stress testing

➢Step 1: Calculate **K** value at different temperature

## Graph **Log Concentration** vs **Time**



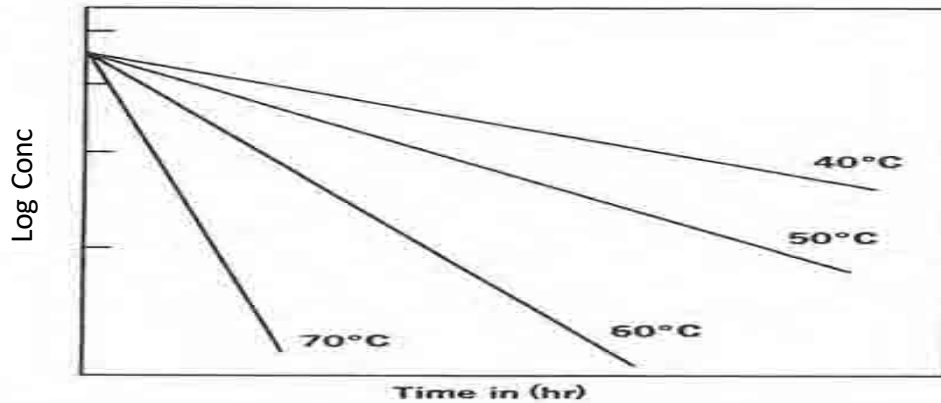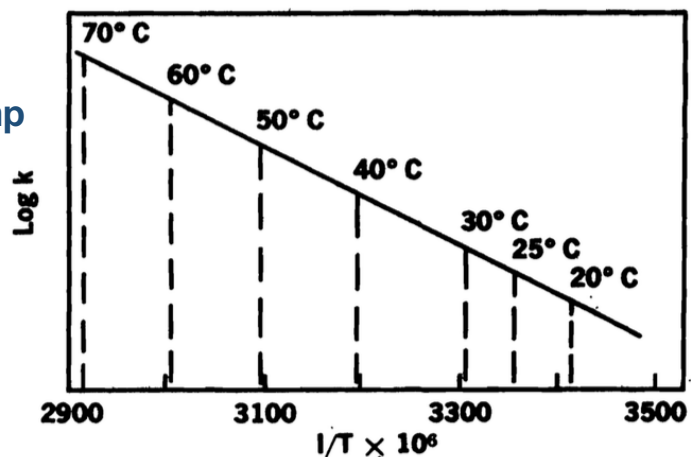**Fig. 14—19.** Accelerated breakdown of a drug in aqueous solution at elevated temperature.

# Steps of stress testing

➢Step 2: Calculate **K$_{25}$** from:

Graph **Log K** vs **1/Abs Temp**

➢Step 3: Calculate **t$_{90\%}$** from equation :

$$t_{90\%} = 0.105 / K_{25}$$



**Fig. 12—21.** Arrhenius plot for predicting drug stability at room temperatures.
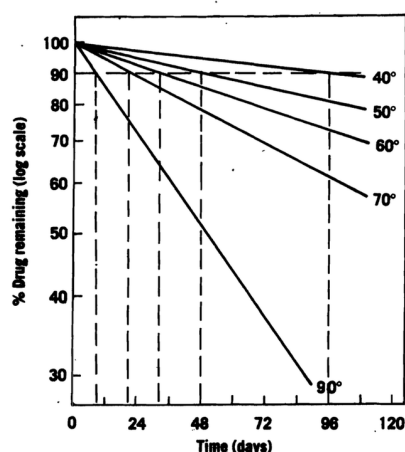
# Steps of stress testing

> Another method:



**Fig. 12–22.** Time in days required for drug potency to fall to 90% of original value. These times, designated $t_{90}$, are then plotted on a log scale in Figure 12–23.
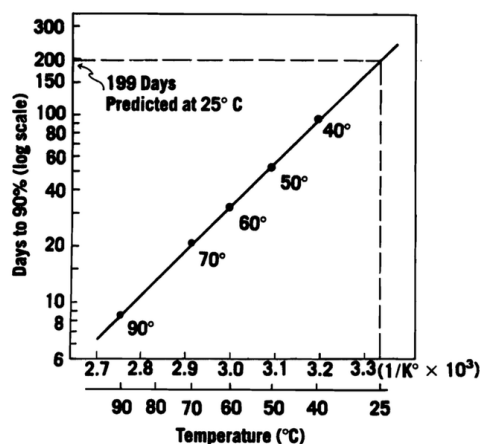
**Fig. 12–23.** A log plot of $t_{90}$ (i.e., time to 90% potency) on the vertical axis against reciprocal temperature (both Kelvin and centigrade scales are shown) on the horizontal axis.

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### EXAMPLE 14–14

**Expiration Dating**

The initial concentration of a drug decomposing according to first-order kinetics is 94 units/mL. The specific decomposition rate, $k$, obtained from an Arrhenius plot is $2.09 \times 10^{-5}$ hr$^{-1}$ at room temperature, 25°C. Previous experimentation has shown that when the concentration of the drug falls below 45 units/mL it is not sufficiently potent for use and should be removed from the market. What expiration date should be assigned to this product?
We have

$$t = \frac{2.303}{k} \log \frac{c_0}{c}$$

$$t = \frac{2.303}{2.09 \times 10^{-5}} \log \frac{94}{45} = 3.5 \times 10^4 \text{ hr} \cong 4 \text{ years}$$

# 2) Solvent effect

- The equation that describes the effect of the dielectric constant, ε, on the rate of hydrolysis is:

$$\log k = \log k_{\varepsilon=\infty} - Kz_A z_B/\varepsilon$$

- Where **K** is a constant for a particular reaction at a given temperature, $z_A$ and $z_B$ are the charge numbers of the two interacting ions and $k_{\varepsilon=\infty}$ is the rate constant in a theoretical solvent of infinite dielectric constant.

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- Intercept = $k_{\varepsilon=\infty}$
- Slope = $Kz_A z_B$
- a, ions of opposite charge, b, ion and uncharged molecule and c, ions of similar charge.

- Table 14-4: solvent polarity



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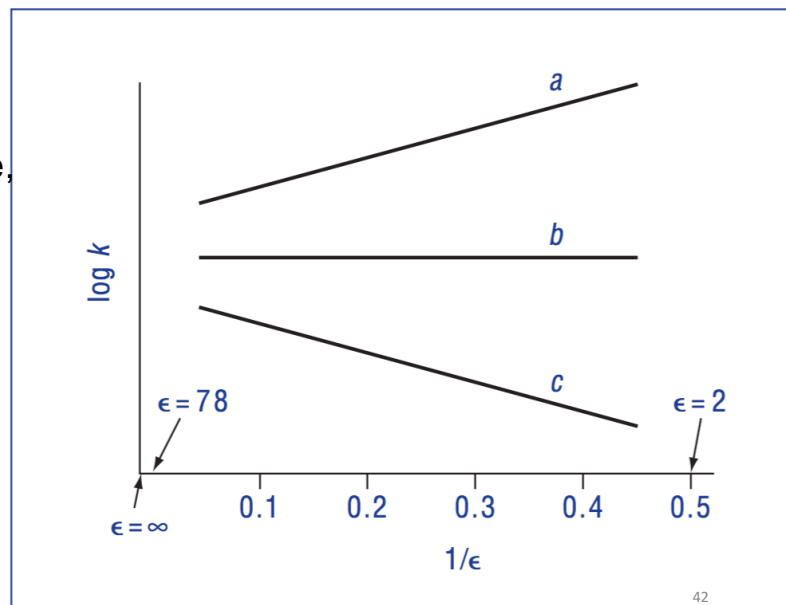
- The gradient will be positive if the drug ion and the interacting ion are of opposite signs and therefore the choice of a non-polar solvent will ………. decomposition. "**Case a**"

- **Case b** ?

- The gradient will be negative when the charges on the drug ion and the interacting species are the same. This means that if we replace the water with a solvent of lower dielectric constant then we will achieve the desired effect of reducing the reaction rate. "**Case c**"

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## 3) Ionic strength

- The equation which describes the influence of electrolyte on the rate constant is the Brønsted–Bjerrum equation:

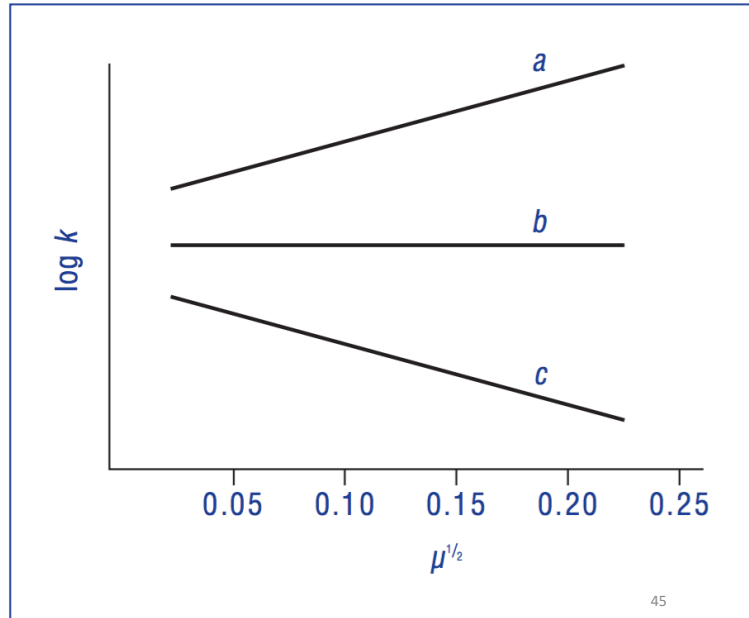$$\log k = \log k_0 + 2A z_A z_B \sqrt{\mu}$$

- where $z_A$ and $z_B$ are the charge numbers of the two interacting ions, **A** is a constant for a given solvent and temperature and **µ** is the ionic strength.

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- Intercept= **log $k_0$**
- Slope = **$2Az_Az_B$**
- **a**: ions of similar charge,
- **b**: ion and uncharged molecule and
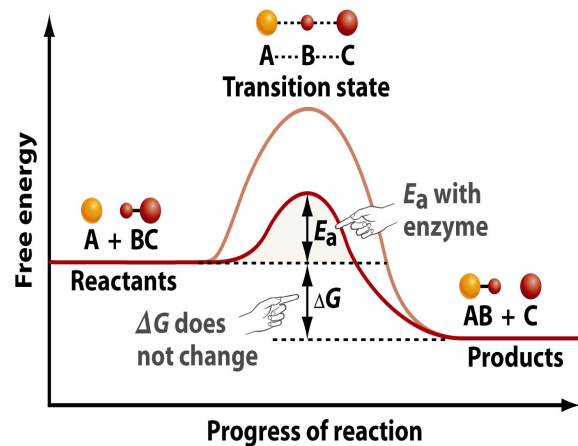- **c**: ions of opposite charge.



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- The gradient will be positive (i.e. the reaction rate will be increased by electrolyte addition) when reaction is between ions of similar charge, for example, the acid-catalysed hydrolysis of a cationic drug ion. "**Case a**"

- **Case b** ?

- The gradient will be negative (i.e. the reaction rate will be decreased by electrolyte addition) when the reaction is between ions of opposite charge, for example, the base-catalysed hydrolysis of positively charged drug species. "**Case c**"

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# Catalysis

- Catalysis is a substance that increase the reaction rate without being structurally changed.

- Negative catalysis ( also called Inhibitors) is . . . . . .



A····B····C
**Transition state**

$E_a$ with enzyme

A + BC
**Reactants**

$E_a$

$\Delta G$ does not change

$\Delta G$

AB + C
**Products**

**Progress of reaction**

Figure 3-21  Biological Science, 2/e          © 2005 Pearson Prentice Hall, Inc.

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# 4) Effect of pH

1. Specific acid-base catalysis : effect of hydrogen and hydroxyl ions.

2. General acid-base catalysis : effect of other components of the buffer system

- The general equation for these two effects is:

$$k_{obs}=k_0+ k_{H^+} [H^+] + k_{OH^-} [OH^-] + k_{HX} [HX] + k_{X^-} [X^-]$$

- where $k_{obs}$ is the experimentally determined hydrolytic rate constant, $k_0$ is the uncatalysed, $k_H+$ and $k_{OH}-$ are the specific acid and base catalysis rate constants respectively, $k_{HX}$ and $k_{X}-$ are the general acid and base catalysis rate constants respectively and [HX] and [X$^-$] denote the concentrations of protonated and unprotonated forms of the buffer.

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# Specific Acid-Base catalysis

The rate constants for specific acid and base catalysis can be determined from the **linear plots** obtained when the corrected experimental rate constants $k_{obs}$ are plotted against the pH
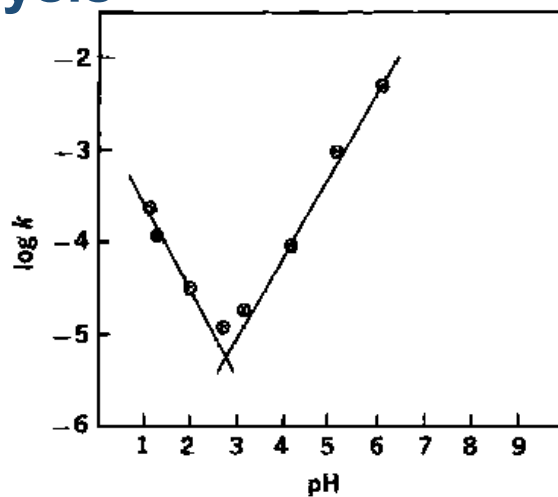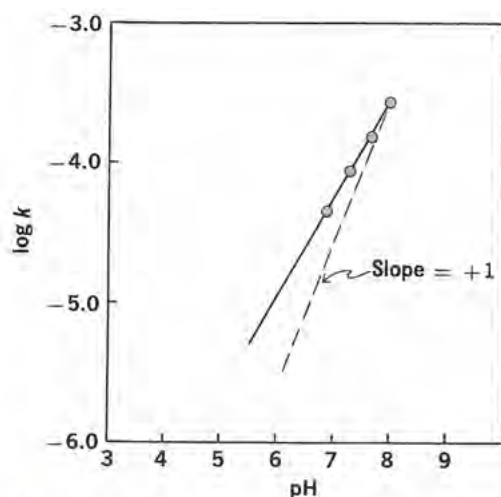


Esters + H ( acid)

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**Fig. 14–9.** Rate–pH profile of a reaction susceptible to general base catalysis. (From E. R. Garrett, J. Pharm. Sci. **49**, 767, 1960. With permission.)

- Complex pH rate profiles are seen when the ionisation of the drug changes over the pH of measurement because of the differing susceptibility of the unionised and ionised forms of the drug to hydrolysis.

- Therefore we have to select the best pH for maximum stability of the drug in the liquid dosage form ( Oral, Injectable, Ophthalmic) and maintaining pH constant by addition of buffering agent
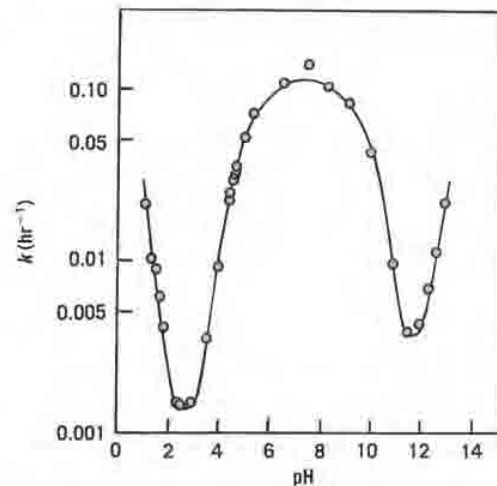


Fig. 14–11. The pH profile for the hydrolysis of hydrochlorothiazide. (From J. A. Mollica, C. R. Rohn, and J. B. Smith, J. Pharm. Sci. 58, 636, 1969. With permission.)

# 5) Oxygen
- The susceptibility of a drug to the presence of oxygen can be tested by comparing its stability in ampoules purged with oxygen to that when it is stored under nitrogen.
- Drugs which have a higher rate of decomposition when exposed to oxygen can be stabilised by replacing the oxygen in the storage container with nitrogen or carbon dioxide. These drugs should also be kept out of contact with heavy metals and should be stabilised with antioxidants.

# 6) Light
- The susceptibility of a drug to light can readily be tested by comparing its stability when exposed to light to that when  stored in the dark.
- Photolabile drugs should be stored in containers of amber glass and, as an added precaution, should be kept in the dark.

## Stability of Pharmaceuticals

• Pharmaceutical decomposition can be classified as hydrolysis, oxidation, isomerization, epimerization, and photolysis.

• These processes may affect the stability of drugs in liquid, solid, and semisolid products.

• the ingredients of dosage forms and environmental factors have an effects on the chemical and physical stability of pharmaceutical preparations.

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# Examples

➢**Ampicillin**
  ➢Hydrolysis by first order kinetics
  ➢Specific and general acid–base catalysis
  ➢Sucrose increase hydrolysis
  ➢Alcohol reduce hydrolysis by reducing dielectric constant

➢**Chloramphenicol**
  ➢Degradation was low and independent of pH (2-7)
  ➢General acid-base catalysed by phosphate, acetic acid and citrate buffer.

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➢**Doxorubicin**

    ➢It chelates with metal ions, self-associates in concentrated solutions, adsorbs to surfaces such as glass, and undergoes oxidative and photolytic decomposition.

    ➢Decomposition was pseudo-first order.

➢**Erythromycin**

    ➢It has the disadvantage of degradation in an acidic environment.

    ➢Ester salt was formulated to protect the drug.

➢**Ascorbic acid**

    ➢Act as anti-oxidant and might lead to reduce rate of oxidation

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# Thanks for your attention

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