3. Kinetics, Reaction Rates and Drug Stability

3.1 Introduction

- Kinetics comes form the Greek word kinesis meaning movement.

- Reaction kinetics is the "study of rate of chemical change and the way in which this rate is influenced by the conditions of concentration of the reactants, products, and other chemical species which may be present, and by factors such as solvent, pressure, and temperature".

3.1 Introduction

- Factors affecting reaction rate:
  1- Nature of reactants – major factor
  2- Concentration of reactants
  3- concentration of catalysts
  4- Temperature

3.1. Introduction:

- One of the most common applications of kinetics in pharmaceutics is the study of the rates of drug degradation in pharmaceutical products and the determination of the proper shelf lives and storage conditions for these products.

- The stability of the active ingredient of a drug is a major criterion in the rational design and evaluation of drug dosage forms. Problems with stability can determine whether a given formulation is accepted or rejected.

1. Extensive chemical degradation of the active ingredient can cause substantial loss of the active ingredient from the dosage form.
2. Instability of the drug product can cause decreased bioavailability
3. Chemical degradation can produce a toxic product.

3.2. Rates and Orders of Reactions:

- The rate of a reaction, or degradation rate, is the velocity with which the reaction occurs.
- The rate or speed of a reaction can be expressed as the ratio of change in concentration of a reactant (product) to a change in time.
- Rate of a chemical reaction = $\frac{dc}{dt}$

$$= \frac{mole/Liter}{Second} = mol.L^{-1}.Sec^{-1}$$

- *dc* is the change (decrease or increase) in concentration over the time period *dt*.

3.2. Rates and Orders of Reactions:

- **The order of a reaction** is the way in which the concentration of a drug or reactant in a chemical reaction affects the rate.
- The rate of a simple A $\longrightarrow$ B reaction can be written as

$$\textbf{rate}\ \alpha\ [A]^{a}$$

- Where *a* is called the order of the reaction
- *a* is 1 in first order reactions, second and third order reactions are possible too.
- *a* could be 0 in case of a zero order reaction.
- In a more complex reaction A+B $\longrightarrow$ C

the rate becomes:

$$\textbf{Rate}\ \alpha\ [A]^{a}[B]^{b}$$

- The overall order of the reaction is the sum of exponents (a+b)

3.2. Rates and Orders of Reactions:

- The order with respect to one of the reactants is the exponent of that particular concentration term.
- The exponents a and b ***don’t have a direct relation*** with the coefficients in the balanced chemical equation for a reaction.
- The value of the exponents as well as the overall order can only be determined from experiment (i.e. The order with respect to each reactant cannot be deduced from stoichiometric equation of the reaction).

3.2. Rates and Orders of Reactions:

$$\text{Rate} = K\,[A]^{a}$$
$$\text{Rate}=K\,[A]^{a}[B]^{b}$$

- K is the rate constant of the reaction.
- The reaction rate constant, k, is a numerical expression of the effect of the nature of reactants and temperature on reaction rate.

3.2. Rates and Orders of Reactions:

- To determine the order of the reaction, we change the concentration of one reactant while keeping the concentrations of the others constant.

Experiment	Initial concentrations		Rate of AB Formation (mol/L.Sec)
	A	B	
1	0.1	0.1	12
2	0.1	0.2	24
3	0.1	0.3	36
4	0.2	0.1	48
5	0.3	0.1	108

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1	0.1	0.1	12
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5	0.3	0.1	108

$$Rate=K\,[A]^{a}[B]^{b}$$

$$\frac{Rate\ 2=K\,[A]^{a}[B]2^{b}}{Rate1=K\,[A]^{a}[B]\,1^{b}}$$

$$\frac{Rate\ 2}{Rate1}=\frac{[B]2^{b}}{[B]1^{b}}$$

$$\frac{24}{12}=\frac{0.2^{b}}{0.1^{b}}$$

$$2=2^{b}\longrightarrow\boxed{b=1}$$

Experiment	Initial concentrations		Rate of AB Formation (mol/L.Sec)
	A	B	
1	0.1	0.1	12
2	0.1	0.2	24
3	0.1	0.3	36
4	0.2	0.1	48
5	0.3	0.1	108

$$\text{Rate} = K\,[A]^{a}[B]^{b}$$

$$\frac{\text{Rate 2} = K\,[A]\,2^{a}[B]^{b}}{\text{Rate1} = K\,[A]1^{a}[B]^{b}}$$

$$\frac{\text{Rate 2}}{\text{Rate1}} = \frac{[A]2^{a}}{[A]1^{a}}$$

$$\frac{48}{12} = \frac{0.2^{a}}{0.1^{a}}$$

$$4 = 2^{a} \longrightarrow \boxed{a = 2}$$

3.2. Rates and Orders of Reactions:

- The rate law is:

$$\text{Rate} = K\,[A]^{a}[B]^{b}$$

- Now we look at the change in the rate as we change [B] while [A] is constant.
- Looking at experiments 1,2 and 3, we see that the rate is doubled when we doubled [B] and tripled when we tripled [B].
- The exponent b must be equal to 1 to account for that.
- The reaction is first order with respect to B

3.2. Rates and Orders of Reactions:

- Now look at the experiments 1, 4 and 5 where [A] changes while [B] is kept constant.
- The rate increases by a factor of 4 when [A] is doubled.
- The rate increases by factor of 9 when [A] is tripled.
- The order or power that could get such results is 2.
- The reaction is second order with respect to A.
- The overall reaction is a third order reaction.

3.2. Rates and Orders of Reactions:

- Now the rate law is:

$$Rate=K\,[A]^{2}[B]^{1}$$

- The rate constant can be calculated from any of the experiments:

$$12\ mol.L^{-1}.Sec^{-1}=k(0.1mol.L^{-1})^{2}(0.1mol.L^{-1})$$

$$k=12x10^{-3}\ L^{2}.mol^{-2}.Sec^{-1}$$

3.3. Units of Rate Constants:

- For a zero order reaction:

$$\frac{dc}{dt} = k[A]^0$$

$$k = \frac{mole}{L.Sec.}$$

- For a first order reaction:

$$\frac{dc}{dt} = k[A]^1$$

$$k = \frac{dc}{dt} \times \frac{L}{mole} = \frac{mole}{L.Sec.} \times \frac{L}{mole} = \frac{1}{Sec.} = Sec.^{-1}$$

3.3. Units of Rate Constants:

- For a second order reaction

$$\frac{dc}{dt} = k[A]^2$$

$$k = \frac{dc}{dt}[A]^{-2}$$

$$k = \frac{mole}{L.Sec.} \times \frac{L^2}{mole^2} = \frac{L}{mole.Sec.}$$

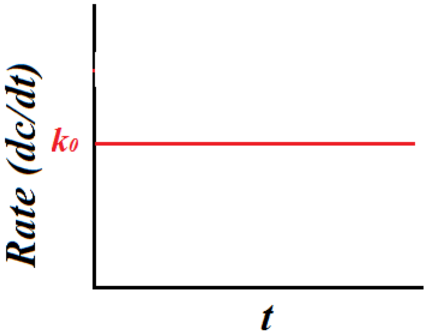
3.4. Zero – Order Reactions:

- The rate law for a zero-order reaction is:

$$\frac{dc}{dt} = k_0[A]^0 = k_0$$

C_t: remaining conc. at certain time.
t: time required to reach certain conc.
t_{50} and t_{90}

- The rate in such reactions is constant and independent of the concentrations of the reactants. Other factors, such as absorption of light in certain photochemical reactions, determine the rate.



3.4. Zero – Order Reactions:

- In zero order reactions, the drug concentration changes with respect to time at a constant rate.
- By integrating the rate law between the initial concentration of the reactant (C_0) and the concentration at time t (C_t).

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

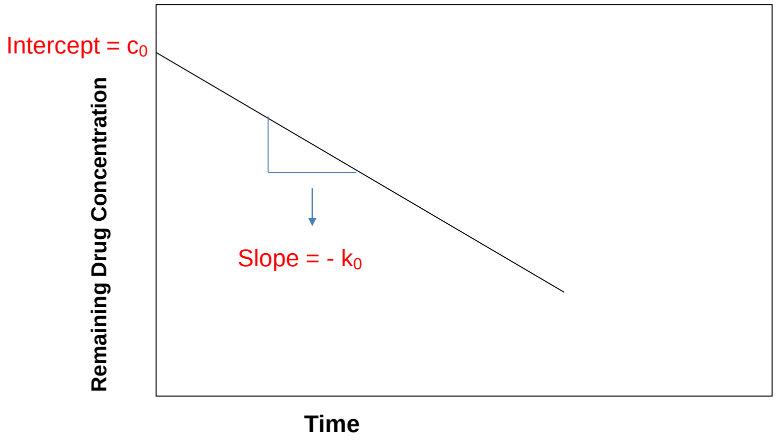
$$\int_{C_0}^{C_t} dc = -k_0 \int_{t_0}^{t} dt$$

$$c_t - c_0 = -k_0 t$$

$$c_t = c_0 - k_0 t$$

c_0: initial concentration at t_0
c_t: remaining conc. at time t.

3.4. Zero – Order Reactions:



3.4. Zero – Order Reactions:

- By integrating the rate law between the initial concentration of the product (C_0) and the concentration at time t (C_t).

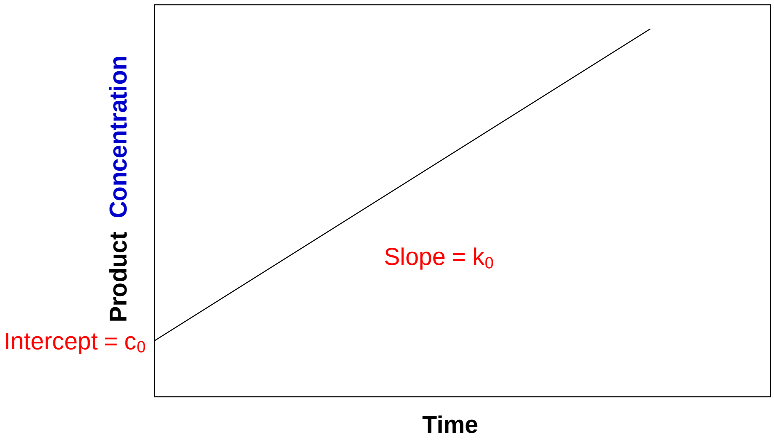
$$\frac{dc}{dt} = k_0$$

$$\int_{C_0}^{C_t} dc = k_0 \int_{t_0}^{t} dt$$

$$c_t - c_0 = k_0 t$$

$$c_t = c_0 + k_0 t$$

3.4. Zero – Order Reactions:



3.4. Zero – Order Reactions:

- The half life of a drug in a formulation is the time required for the amount (conc.) of the drug to drop to half its original value.

$$c_t = c_0 - k_0 t$$

$$\frac{1}{2}c_0 = c_0 - k_0 t_{0.5}$$

$$\frac{1}{2}c_0 = k_0 t_{0.5}$$

$$t_{0.5} = \frac{c_0}{2k_0}$$

3.4. Zero – Order Reactions:

- Shelf life: The time required for a drug to degrade to 90% of its original concentration ($t_{90\%}$) is also important. This time represents a reasonable limit of degradation for the active ingredient. The $t_{90\%}$ can be calculated as:

$$c = c_0 - k_0 t$$

$$0.9c_0 = c_0 - k_0 t_{90}$$

$$t_{90} = \frac{c_0}{10k_0} \qquad t_{90} = \frac{t_{0.5}}{5}$$

- Note that $t_{0.5}$ and t_{90} in zero-order reactions are concentration dependent.

3.4. Zero – Order Reactions:

A drug decomposes by zero-order kinetics with a rate constant of 2 mg $mL^{-1}month^{-1}$. If the initial concentration is 100 mg mL^{-1}

1. What is the shelf life?

$$t_{90} = \frac{c_0}{10k_0}$$

$t_{90\%}$ = 5 month

2. What is the half life?

$$t_{0.5} = \frac{c_0}{2k_0}$$

$t_{0.5}$ = 25 month

3. What is the half life if the initial concentration is 50 mg mL^{-1}?

$$t_{0.5} = \frac{c_0}{2k_0}$$

$t_{0.5}$ = 12.5 month

4. Calculate the drug remaining concentration after 1 year.

$C = C_o - Kt$

= 100 mg/ml – 2 mg/ml.month * 12 month

C = 76 mg/mL

5. What time is required to reach a drug concentration of 80 mg mL^{-1}?

$C = C_o - Kt$

80 = 100 – 2t

t = 10 months

3.5. First Order Reactions:

- The rate law for the first order reaction is:

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

C_t: remaining conc. at certain time.
t: time required to reach certain conc.
t_{50} and t_{90}

$$-\frac{d[H_2O_2]}{dt} = k[H_2O_2]$$

- Integrating the equation between c_0 (concentration at t=0) and c_t (concentration at time t) gives:

$$\frac{dc}{[H_2O_2]} = -kdt$$

$$\int_{C_0}^{C_t} \frac{dc}{[H_2O_2]} = -k\int_0^t dt$$

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

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

3.5. First Order Reactions:

- Converting to common log to the base 10 we get:

$$\log c = \log c_0 - \frac{kt}{2.303}$$

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

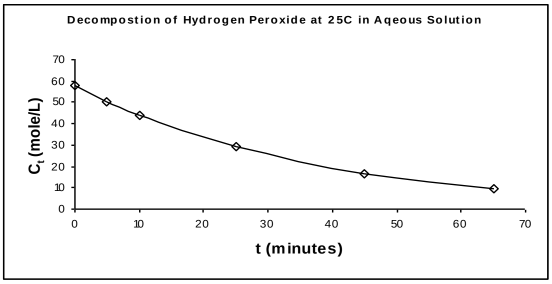
- The previous equations can be converted to exponential forms:

$$c = c_0 e^{-kt}$$

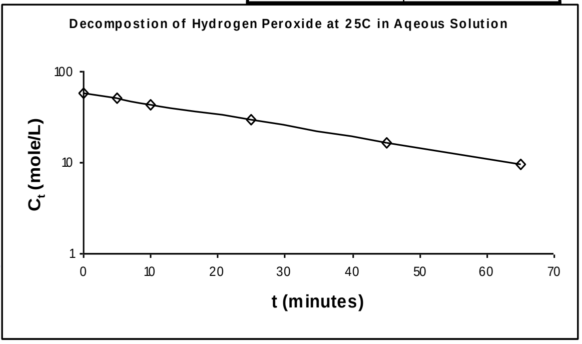
$$c = c_0 10^{\frac{-kt}{2.303}}$$

- The equations express the fact that in a first order reaction, the concentration decreases exponentially with time.

- In a first-order reaction, rate depends on the first power of a single reactant.



t (minutes)	**C_t (M)**
0	57.90
5	50.40
10	43.90
25	29.10
45	16.70
65	9.60



The slope of the straight line is -k/2.303

The intercept is c_0 (log y axis)

3.5. First Order Reactions:

- To calculate the half life of a first order reaction:

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

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

$$\ln \frac{c_0}{c} = kt$$

$$\ln \frac{c_0}{0.5 c_0} = kt_{0.5}$$

$$\ln 2 = kt_{0.5}$$

$$t_{0.5} = \frac{0.693}{k}$$

3.5. First Order Reactions:

- In order to determine t_{90},

$$kt_{90} = 2.303\log\left(\frac{c_0}{0.9c_0}\right) = 0.105$$

Thus

$$t_{90} = \frac{0.105}{k}$$

- Both $t_{0.5}$ and t_{90} are concentration-independent. Thus, for $t_{0.5}$, it take the same amount of time to reduce the concentration of the drug from 100 mM to 50mM as it does from 50mM to 25mM.

3.5. First Order Reactions:

A drug decomposes by first-order kinetics with a rate constant of 0.01 month^{-1}. If the initial concentration is 100 mg mL^{-1}

1. What is the shelf life?

$$t_{90} = \frac{0.105}{k}$$

$t_{90\%}$ = 10.5 month

2. What is the half life?

$t_{0.5}$= 0.693/ k

$t_{0.5}$ = 69.3 month

3. What is the half life if the initial concentration is 50 mg mL^{-1}?

$t_{0.5}$= 0.693/ k

$t_{0.5}$ = 69.3 month

4. Calculate the drug remaining concentration after 1 year.

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

C = 88.7 mg/mL

5. What time is required to reach a drug concentration of 80 mg mL^{-1}?

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

t = 22.3 months

6. What time is required to reach a drug concentration of 60 mg mL^{-1}?

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

t = 51.1 months

3.5. First Order Reactions:

Example (14-3): Martin’s 6th ed.:

c_o= 57.9; after 65 min: c= 9.6

a) Calculate k:

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

k= (2.303/65) log (57.9/9.6)= 0.0277min^{-1}

b) How much hydrogen peroxide remained undecomposed after 25 min?

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

0.0277= (2.303/25) log(57.9/c); c= 29.01

3.5. First Order Reactions:

Example (14-4): Martin’s 6th ed.:

c_o= 500; after 40 days: c= 300; assuming first order decomposition, **calculate $t_{0.5}$**

$$t_{0.5}= 0.693/ k$$

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

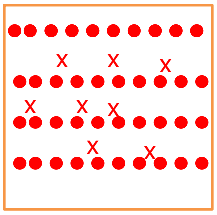
k= (2.303/40) log(500/300)= 0.0128 day^{-1}

$t_{0.5}$= 0.693/ k

$t_{0.5}$ =0.693/0.0128= 54.1 days

Apparent zero-order reactions (suspension):

- Consider a first order degradation reaction of a drug in solution. The rate of degradation (decline in drug conc.) is proportional to the conc. of the drug: The rate changes with changing conc.



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

- Now consider a suspension where the solid drug is in equilibrium with the drug in solution, the concentration wouldn't change because the solid drug will compensate for the decomposition and so the rate remains constant. As the drug decomposed in solution, more drug is released from the suspended particles so that the concentration is constant. This concentration is the drug's equilibrium solubility in a particular solvent at a particular temperature (*c*).

Apparent zero-order reactions (suspension):

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

$$kc = k_o$$

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

- The rate in this case is called apparent zero order rate.
- The system changes to first-order once all suspended particles have changed to drug in solution.

Apparent zero-order reactions (suspension):

Example (14-2; Martin's 6th ed.):

Solubility of Aspirin= 0.33 g/ 100 ml; c_o= 6.5 g/ 100 ml; k=4.5×10^{-6} sec^{-1}

Calculate k_o and t_{90}

Answer:

k_o= kc
k_o= k[aspirin in solution]
k_o= (4.5×10^{-6}) (0.33)
k_o= 1.5×10^{-6} g/100 ml sec^{-1}

t_{90}= 0.1 c_o/ k_o
t_{90}= 0.1x 6.5/ 1.5×10^{-6}
t_{90}= 4.3×10^{5} sec = 5 days

How many days are required to reach a drug concentration of 0.33 g/100 ml?

$C = C_o - K_o t$
$0.33 = 6.5 - 1.5\times10^{-6}\, t$
$t = 4.1\times10^{6}$ sec
t = 47.6 days.

Practice Questions

- **The rate constant of a zero order reaction is 0.2 mol dm^{-3} h^{-1}. If the concentration of the reactant after 30 min is 0.05 mol dm^{-3}. what is the initial concentration?**

$C = C_o - Kt$
$C_o = C + Kt$
C_o= 0.05 mol dm^{-3}+ 0.2 mol dm^{-3} h^{-1} x 0.5 h
C_o= 0.15 mol dm^{-3}

What is the half life?

$t_{0.5}= C_0/ 2 K_0$
$t_{0.5}$ = 0.15/2 x 0.2
$t_{0.5}$ = 0.375 h

Practice Questions

- **A drug has the initial concentration of 5.0 x 10^{-3} g cm^{-3} in aqueous solution. After 24 months, the concentration drops to 3.48 x 10^{-3} g cm^{-3}. This degradation process is known to follow first-order kinetics. What is the rate constant for this reaction:**

$$k = \frac{2.303}{t} \log \frac{C_0}{C}$$

k= (2.303/24) log(5.0 x 10^{-3} /3.48 x 10^{-3})
k = 0.0151 $month^{-1}$

What is the half life?

$t_{0.5}$= 0.693/ k
$t_{0.5}$ =0.693/0.0151= 45.9 months

Calculate the drug remaining concentration after 1 year.

$$k = \frac{2.303}{t} \log \frac{C_0}{C}$$

0.0151= (2.303/12) log(5.0 x 10^{-3} /C)
C= 4.17 x 10^{-3} g cm^{-3}

3.6. Second Order Reactions:

- Second order reactions can be simply either:

1. Degradation of a reactant following 2nd order kinetics:

$$A \longrightarrow B$$

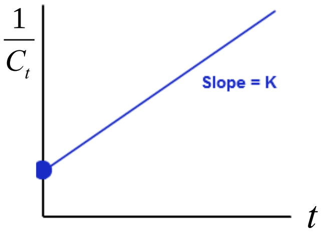
The rate law of this second order reaction is

$$-\frac{d[C]}{dt} = k[C]^2$$

C: concentration of remaining reactant at any time
K: second order reaction rate constant
C_0: Initial concentration of reactant

$$\int_{C_0}^{C_t} \frac{d[C]}{[C]^2} = -k \int_0^t dt$$

$$\frac{1}{C_t} = \frac{1}{C_0} + kt$$



In second order Rx: the equation shows linear relationship between $\frac{1}{C_t}$ vs. t with a slope of k and intercept of $\frac{1}{C_0}$

3.6. Second Order Reactions:

- The half-life of a second order reaction is:

$$\frac{1}{C_t} = \frac{1}{C_0} + kt$$

$$\frac{1}{0.5C_0} = \frac{1}{C_0} + kt_{0.5}$$

$$t_{0.5} = \frac{1}{kC_0}$$

500 mg	250 mg

$$-\frac{d[C]}{dt} = k[C]^2$$

$$t_{0.5} = \frac{1}{kC_0}$$

If conc. Increased by two times, the rate increases by 4 times (but half life decreases to half)

Calculate the t_{90} of a second order reaction.

$t_{90\%}$ = = $0.111/KC_0$

3.6. Second Order Reactions:

2. A reaction between A and B with overall 2^{nd} order rxn.

$$A + B \longrightarrow AB$$

The rate law of this second order reaction is

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

•If A_0 and B_0 are the initial concentrations of A and B, and x is the concentration of each species **reacting** at time *t*, then the rate is:

$$\frac{d[x]}{dt} = k[A_0 - x][B_0 - x]$$

3.6. Second Order Reactions:

$$\frac{d[x]}{dt} = k[A_0 - x][B_0 - x]$$

$$if: A_0 = B_0$$

$$\frac{d[x]}{dt} = k[A_0 - x]^2$$

$$\int_0^x \frac{d[x]}{[A_0 - x]^2} = -k\int_0^t dt$$

$$\frac{1}{A_t} = \frac{1}{A_0} + kt$$

$$\frac{1}{B_t} = \frac{1}{B_0} + kt$$

$$t_{0.5} = \frac{1}{kA_0} = \frac{1}{kB_0}$$

Example 14-5 (Martin's 6th ed.):

$CH_3COOC_2H_5$ + NaOH⟶ CH_3COONa + C_2H_5OH

$A_o=B_o=$ 0.01 M; during 20 min: change in NaOH was (x= 0.00566 M).

1) Compute the rate constant (6.52 liter/mol.min)

2) Half life (15.3 min)

Second – Order Reactions:

A drug decomposes by second-order kinetics with a rate constant of 0.02 mL mg^{-1} month^{-1}. If the initial concentration is 100 mg mL^{-1}

1. What is the half life?

$t_{0.5} = 1/KC_0$

$t_{0.5} = 1/0.02*100$

$t_{0.5} = 0.5$ month

2. What is the shelf life?

$t_{90\%} = 0.111/KC_0$

$t_{90\%} = 0.111/0.02*100$

$t_{90\%} = 0.056$ month

3. What is the half life if the initial concentration is 50 mg mL^{-1}?

$t_{0.5} = 1/KC_0$

$t_{0.5} = 1/0.02*50$

$t_{0.5} = 1$ month

4. Calculate the drug remaining concentration after 1 month.

$1/C_t = 1/C_0 + kt$

$1/C_t = 1/100 + 0.02 * 1$

$1/C_t = 0.03$

$C_t = 33.3$ mg mL^{-1}

5. What time is required to reach a drug concentration of 80 mg mL^{-1}?

$1/C_t = 1/C_0 + kt$

$1/80 - 1/100 = 0.02 * t$

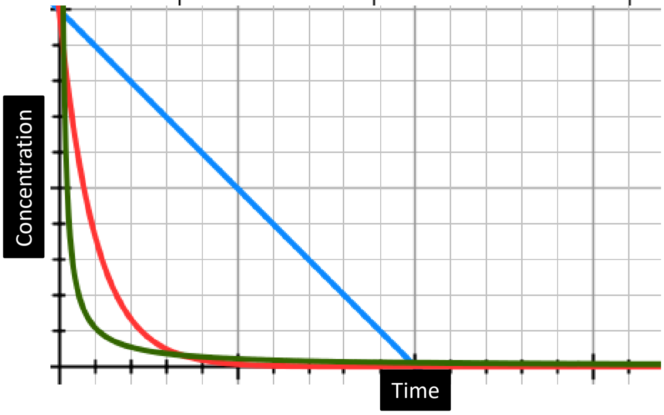
$0.0025 = 0.02 * t$

t= 0.125 month

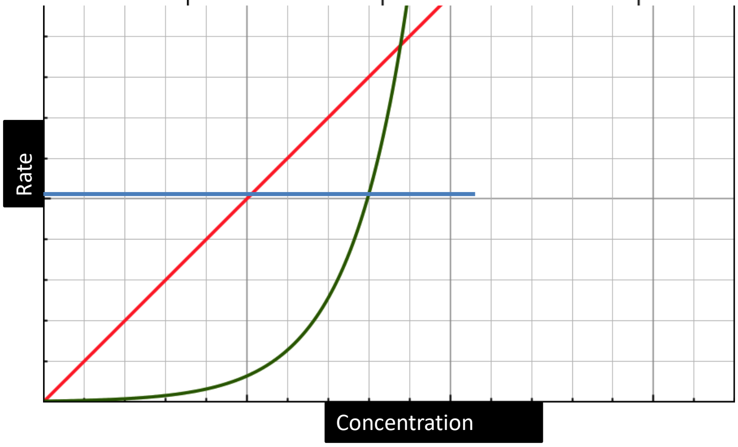
t= 3.75 days

Rx Order	0	1	2
Rate Eq	$\frac{d[C]}{dt} = -k_0$	$\frac{d[C]}{dt} = -k_1[C]$	$\frac{d[C]}{dt} = -k_2[C]^2$
Integrated Rate Eq	$C_t = C_0 - k_0 t$	$\ln C_t = \ln C_0 - k_1 t$	$\frac{1}{C_t} = \frac{1}{C_0} + k_2 t$
Half-life Eq	$t_{0.5} = \frac{C_0}{2k_0}$	$t_{0.5} = \frac{0.693}{k_1}$	$t_{0.5} = \frac{1}{k_2 C_0}$

	Zero	First	Second
Rate Eq	$\frac{d[C]}{dt} = -k_0$	$\frac{d[C]}{dt} = -k_1[C]$	$\frac{d[C]}{dt} = -k_2[C]^2$



	Zero	First	Second
Rate Eq	$\frac{d[C]}{dt} = -k_0$	$\frac{d[C]}{dt} = -k_1[C]$	$\frac{d[C]}{dt} = -k_2[C]^2$



3.10. Influence of Temperature on Reaction Rates:

- Reaction rates are expected to be proportional to the number of collisions per unit time.
- As temperature increases, the number of collisions increases. Hence, the reaction rate is expected to increase with increasing temperature.
- Speed or rate of many reactions increase about two to three times with each 10° rise in temperature.
- An increase in temperature causes an increase in the reaction rate. This effect or relationship is expressed in the equation first suggested by Arrhenius.

3.10. Influence of Temperature on Reaction Rates:

- The effect of temperature on reaction rate is given by the Arrhenius Equation:

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

- By taking the log of both sides, the equation transforms into:

$$\log k = \log A - \frac{Ea}{2.303RT}$$

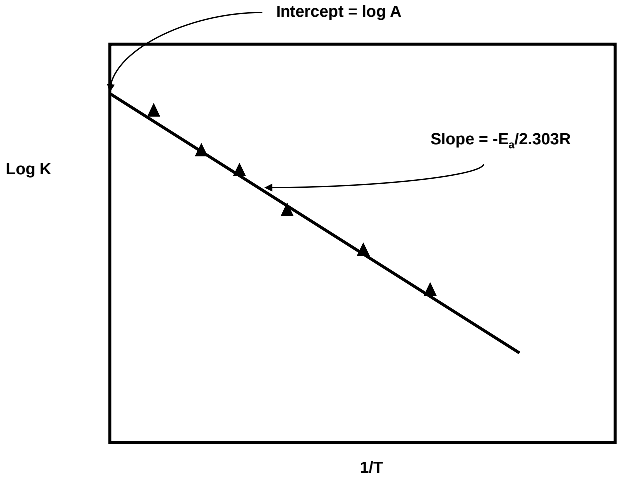
- In which:
  - k is the specific reaction rate
  - A is a constant (Arrhenius or Frequency Factor)
  - E_a is the energy of activation (cal/mol)
  - R is the gas constant (1.987 cal/deg.mol)
  - T is the absolute temperature

3.10. Influence of Temperature on Reaction Rates:

- Arrhenius constant (A) is related to the frequency of molecular collisions in the Collision Theory.

- The activation energy (E_a) is the energy barrier that the reactants must surmount in order to react (energy threshold) or the energy which must be exceeded if the collision of two reactants is to lead to a reaction. As temperature increases, more molecules are activated, and the reaction rate increases; according to the Collision Theory.

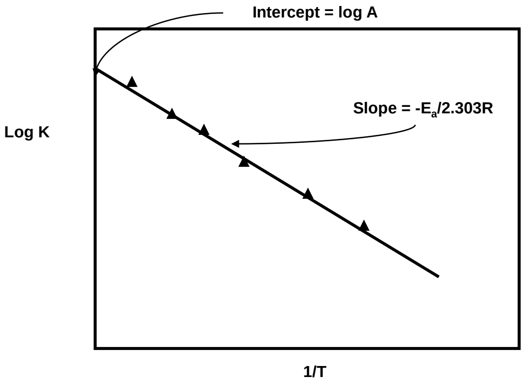
Arrhenius plot



3.10. Influence of Temperature on Reaction Rates:

How to determine A and E_a?

1. Both *A* and E_a can be obtained experimentally by determining *k* at different temperatures and plotting log k against *1/T*.



3.10. Influence of Temperature on Reaction Rates:

How to determine A and E_a? Cont.

2. The best estimation of the Arrhenius constant and activation energy is obtained by performing the reaction at three different temperatures at least (log k vs. 1/T). However two temperatures may be enough to get this estimate.

$$\log k_1 = \log A - \frac{Ea}{2.303RT_1}$$

$$\log k_2 = \log A - \frac{Ea}{2.303RT_2}$$

- Subtracting the two equation gives:

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

3.10. Influence of Temperature on Reaction Rates:

Example (14-7) Martin's 6th ed.;
k_1 at 120°C is 1.173 hr^{-1}; k_2 at 140°C is 4.860 hr^{-1}.

A. Compute Ea

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

Log (4.86/1.173)= [Ea/(2.303*1.987)]*[(413-393)/413*393]
Ea= 22,926 cal/mol= 22.9 kcal/mol

B. Compute A:
At 120°C:

$$\log k_1 = \log A - \frac{Ea}{2.303RT_1}$$

Log(1.173)= logA- (22926/2.303*1.987*393)
logA= 0.0693+ 12.768= 12.84
A= $6.9*10^{12}$ hr^{-1} =$1.9*10^{9}$ sec^{-1}

3.10. Influence of Temperature on Reaction Rates:

Problem 10-24: Martin's 6th ed.:

Cyclophosphamide monohydrate is available as a sterile blend of dry drug and sodium chloride packaged in vials. A suitable aqueous vehicle is added and the sterile powder dissolved with agitation before the product is used parenterally. However, cyclophosphamide monohydrate is only slowly soluble in water, and a hospital pharmacist inquires concerning the advisability of briefly (for 25 min) warming the solution to 70◦C to facilitate dissolution. Assuming that degradation to 90% of the labeled amount is permitted for this compound, and given k at 25◦C = 0.028 day^{-1}, Ea = 25.00 kcal/mole, what answer would you give?

Problem 10-24: Martin's 6th ed.:

Ea = 25000 cal/mol; k_1 at 25°C (298 K) = 0.028 day^{-1},

We should first find k_2 at 70°C (343 K)

$$\log\left(\frac{k_2}{k_1}\right) = \frac{\text{Ea}}{2.303\text{R}}\, x\, \frac{T_2 - T_1}{T_2 T_1}$$

$$\log\left(\frac{k_2}{k_1}\right) = \frac{25000}{2.303 \text{x} 1.987}\, x\, \frac{343 - 298}{343 x 298} = 2.41$$

$$\frac{k_2}{k_1} = \frac{k_2}{0.028} = 254.21$$

$$k_2 = 7.12 day - 1$$

Now, we can determine t90 at 70°C:

$$t_{90} = \frac{0.105}{k} = \frac{0.105}{7.12} = 0.0147 day = 21.24 \text{min}$$

So heating at 70°C for 25 min is not recommended!

Compare that to the shelf life at 25°C? (3.75 days)

3.10. Influence of Temperature on Reaction Rates:

- Solve the following problems which are related to the Arhenius equation from the physical pharmacy book by Martin – 4th edition:
  - Problem 12-9 page 318
  - Problem 12-10 page 318
  - Problem 12-11 page 319
  - Problem 12-12 page 319
  - Problem 12-36 page 323 (assume that the drug degradation follows first order kinetics)

3.10. Influence of Temperature on Reaction Rates:

- If you have the 5th edition of Martin's Physical Pharmacy book, solve the following problems:
  - Problem 15-9 page 728
  - Problem 15-10 page 728
  - Problem 15-11 page 729
  - Problem 15-12 page 729
  - Problem 15-36 page 734 (assume that the drug degradation follows first order kinetics)

3.10. Influence of Temperature on Reaction Rates:

- If you have the 6th edition of Martin's Physical Pharmacy book, solve the following problems:

  - Problem 14-8
  - Problem 14-9
  - Problem 14-10
  - Problem 14-24

3.11. Collision Theory:

- Two species can only react if they come into contact with each other.
- The species have to collide and then they *may* react.

Why *may* ?

- Because they have to:
- ➢ collide the right way around
- ➢ and they have to collide for enough energy for the old bonds to break.

3.11. Collision Theory:

Appropriate orientation:

- Consider a simple reaction involving a collision between two molecules: ethene, $CH_2=CH_2$, and hydrogen chloride, HCl, for example. These react to give chloroethane.

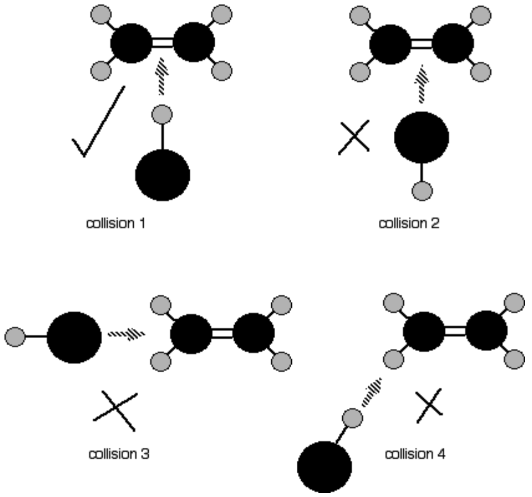
$$CH_2=CH_2 + HCl \longrightarrow CH_3CH_2Cl$$

- As a result of the collision between the two molecules, the double bond between the two carbons is converted into a single bond. A hydrogen atom gets attached to one of the carbons and a chlorine atom to the other.

3.11. Collision Theory:

- The reaction can only happen if the hydrogen end of the H-Cl bond approaches the carbon-carbon double bond. Any other collision between the two molecules doesn't work. They two simply bounce off each other.

3.11. Collision Theory:



3.11. Collision Theory:

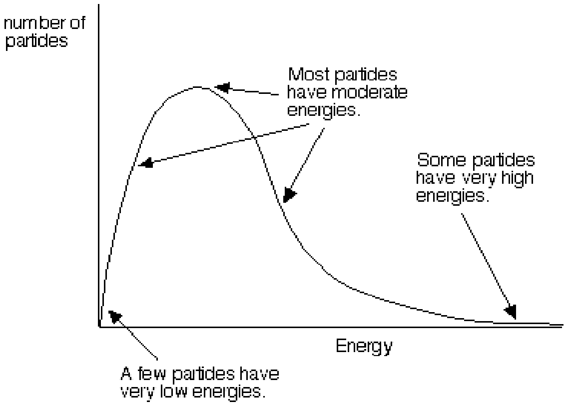
Enough kinetic energy:

- The fraction of molecules having a given kinetic energy is expressed by the *Boltzmann Distribution Law*:

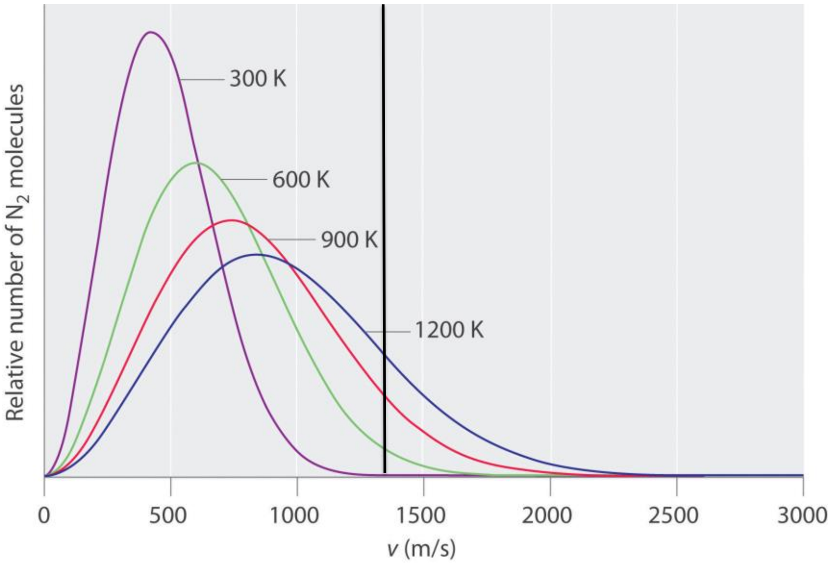
$$f_i = \frac{N_i}{N_t} = e^{-E_i/RT}$$

- Where:
  - N_t is the total number of moles of the reactant
  - N_i is the number of moles of the reactant having a kinetic energy E_i.

3.11. Collision Theory:



Boltzmann Distribution @ various Temperatures



3.11. Collision Theory:

$$\text{Rate} \ \alpha \ N_i$$

- The proportionality constant is divided into two:

$$\text{Rate} = PZ\,N_i$$

  - – P is the steric or probability factor which is included to take into account the probability that a collision occurs with the proper orientation.
  - – Z is the number of collisions per second per cubic cm.

65

3.11. Collision Theory:

- By substituting the Boltzmann distribution law into the rate:

$$\text{Rate} = PZ\,N_i$$

$$f_i = \frac{N_i}{N_t} = e^{-E_i/RT}$$

$$\text{Rate} = (PZe^{-E_i/RT})N_t$$

$$\text{Rate} = kN_t$$

$$k = PZe^{-E_i/RT}$$

$$k = Ae^{-E_a/RT}$$ (Arrhenius equation)

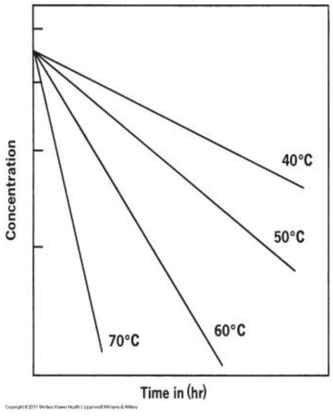
66

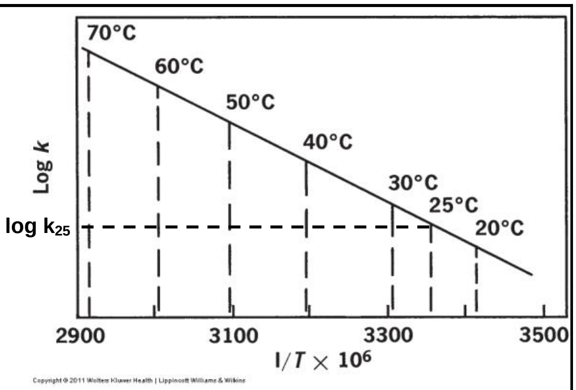
3.11. Collision Theory:

- The collision theory interprets Arrhenius constant (A) as PZ.
- The collision theory interprets Arrhenius activation energy (E_a) as E_i.
- If you heat a substance, the particles move faster and collide more frequently. That will speed up the rate of reaction.

Accelerated Stability Testing:

- Accelerated stability protocols have been developed to reduce the time required to determine the products shelf life at the storage conditions.
- The accelerated stability protocols depends on calculating the rate constant of the degradation reactions at elevated temperature (by plotting some function of concentration vs. time) and then plotting the log k vs. 1/T(in Kelvin).
- The rate at room temperature or storage temperature is then obtained by extrapolating the straight line.





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The rate constant at storage temperature is then used to calculate the shelf life of the drug in the formula (t_{90}).

$$t_{90} = \frac{0.105}{k}$$

Accelerated Stability Testing:

- Limitations of accelerated stability testing based on elevated temperatures:
  - Suitable only if the reaction rate is a thermal phenomenon
  - Not suitable if the degradation depends on diffusion or is a photochemical reaction
  - Not suitable if the degradation is caused by freezing, microbial growth or excessive shaking.
  - Can not be used for products containing suspending or thickening agents that coagulate on heating (Methyl Cellulose).
  - Not suitable for ointments and suppositories that melt at elevated temperature.
  - Some emulsions have higher stability at elevated temperatures.

Shelf life vs. expiry date

Expiry date is the date after which the medicine should not be used.

Example 14-4; Martin's 6th ed.

C_0= 94 units/ml; from Arrhenius plot: at 25°C: k= 2.09 x 10^{-5} hr^{-1}

Experiments showed that when drug falls to 45 units/ml it is not sufficiently potent for use and should be removed from the market.

What expiration date should be assigned for this product?

$$\log c = \log c_0 - \frac{kt}{2.303}$$

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

$$t = \frac{2.303}{2.09x10^{-5}}\log\frac{94}{45} = 3.5x10^4 hr = 4 years$$

Compare your answer to the shelf life? (209 days)

3.13. Catalysis:

- A catalyst is a substance that influence the rate of the reaction without being altered chemically.
- A *Negative Catalyst* decreases the rate of the reaction.
- An inhibitor decreases the rate of the reaction, however it is changed permanently during the reaction.

3.13. Catalysis:

- Catalysts usually act through one of two mechanisms:
  - By combining with the reactant (*substrate*) to produce a complex, which then decomposes to regenerate the catalyst and yield the product. Through this the catalyst accelerates the rate of the reaction by *changing the reaction mechanism and reducing the activation energy.*
  - By producing *free radicals* ($CH_3^{\cdot}$) which initiates fast chain reactions.

3.13. Catalysis:

- Homogenous catalysis:
  - Occurs when the catalyst and the reactants are in the same phase (e.g. acid-base catalysis).
- Heterogeneous catalysis:
  - Occurs when the catalyst and the reactants form separate phases in the mixture (e.g. finely divided solids such as platinum)
  - The catalysis occurs at the surface of the solid and so is called *contact catalysis*.
  - The reactant molecules are adsorbed at various points or active centers of the catalyst, the adsorption weakens the bonds of the reactant molecules and lowers the activation energy.
  - The product diffuses away from the surface after the reaction.

3.14. Specific Acid – Base Catalysis (pH effect):

- Solutions of many drugs undergo accelerated decomposition upon the addition of acids or bases.
- If these drug solutions are buffered, then these reactions may not be accompanied by a significant change in the concentration of hydronium/hydroxyl ions.
- The magnitude of the rate of hydrolytic reaction catalyzed by H^+ and OH^- can vary considerably.

3.14. Specific Acid – Base Catalysis:

The hydrolysis of esters in water at acidic pH is an example of such catalysis:

$$A + H^+ \xrightleftharpoons{k_{eq}} AH^+$$

$$AH^+ + W \xrightarrow{k} P + H^+$$

- A is the ester
- W is the water
- H^+ is the acid
- P is the product

3.14. Specific Acid – Base Catalysis:

- The rate of product formation in such case is:

$$dP/dt= k[AH^+][W]$$

- Now we have to find an expression for the conjugate acid concentration [AH^+].

$$k_{eq}=[AH^+]/[A][H^+]$$

$$[AH^+]=k_{eq}[A][H^+]$$

And

$$dP/dt = kk_{eq}[A][H^+][W]$$

3.14. Specific Acid – Base Catalysis:

$$dP/dt = kk_{eq}[A][H^+][W]$$

- Since the water is present in excess, then the equation reduces into:

$$dP/dt = k_1[A][H^+]$$

Where

$$k_1= kk_{eq}[W]$$

- The presence of [H^+] in the rate equation indicates that the reaction is a specific hydronium ion catalyzed reaction.

3.14. Specific Acid – Base Catalysis:

$$dP/dt = k_1[A][H^+]$$

- We can replace $k_1[H^+]$ by k_{obs}

$$dP/dt = k_{obs}[A]$$

- The rate constant k_{obs} is affected by the pH of the solution and consequently, the rate is affected too.

3.14. Specific Acid – Base Catalysis:

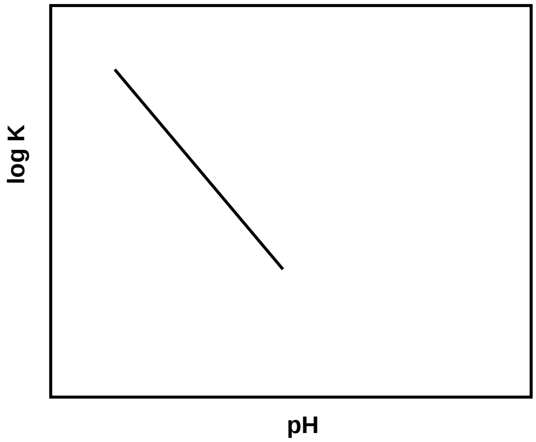
$$k_{obs} = k_1[H^+]$$

- Taking the logarithm of both sides gives us:

$$\log k_{obs} = \log k_1 + \log [H^+]$$
$$\log k_{obs} = \log k_1 - (-\log [H^+])$$
$$\log k_{obs} = \log k_1 - pH$$

- A plot $\log k_{obs}$ of against the pH of the solution gives a straight line with a slope of -1 and an intercept of $\log k_1$.

3.14. Specific Acid – Base Catalysis:



3.14. Specific Acid – Base Catalysis:

- Now if we consider the base catalyzed hydrolysis of the same ester:

$$\mathrm{A + OH- \xrightleftharpoons{\mathit{k_{eq}}} AOH-}$$

$$\mathrm{AOH- + W \xrightarrow{\mathit{k}} P + OH-}$$

- In this case $dP/dt = k\,[AOH\text{-}]\,[W]$

as $[AOH\text{-}] = k_{eq}\,[A]\,[OH\text{-}]$

So $dP/dt = k\,k_{eq}\,[A]\,[OH\text{-}]\,[W]$

$k_2 = k\,k_{eq}\,[W]$

$dP/dt = k_2[A][OH^-]$

Again we can get an apparent first order rate constant (k_{obs})

$$dP/dt = k_{obs}\,[A]$$

Where $k_{obs} = k_2[OH^-]$

3.14. Specific Acid – Base Catalysis:

$$k_{obs} = k_2[OH^-]$$

Since

$$K_w=[H^+]\ [OH^-]$$
$$[OH^-]= K_w/[H^+]$$

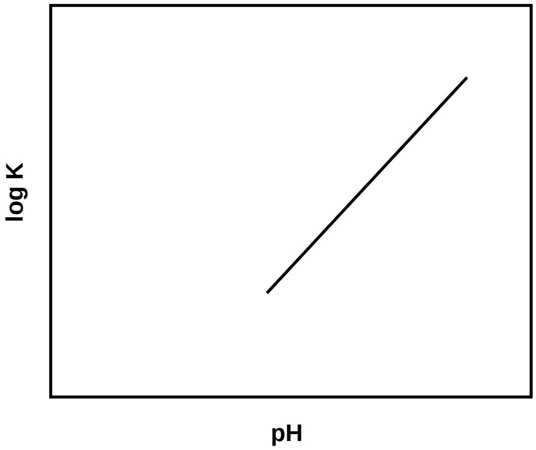
$$k_{obs} = k_2K_w/[H^+]$$

$$\log k_{obs} =\log k_2K_w - \log[H^+]$$

$$\log k_{obs} =\log k_2K_w + pH$$

- A plot of $\log k_{obs}$ against pH would give a straight line with a slope of $+1$ and an intercept of $\log k_2K_w$.

3.14. Specific Acid – Base Catalysis:



3.14. Specific Acid – Base Catalysis:

- The minima in the pH – log k profile is indicative of solvent catalysis (unionized water is considered to be the reacting species).
- In this case the rate equation is:

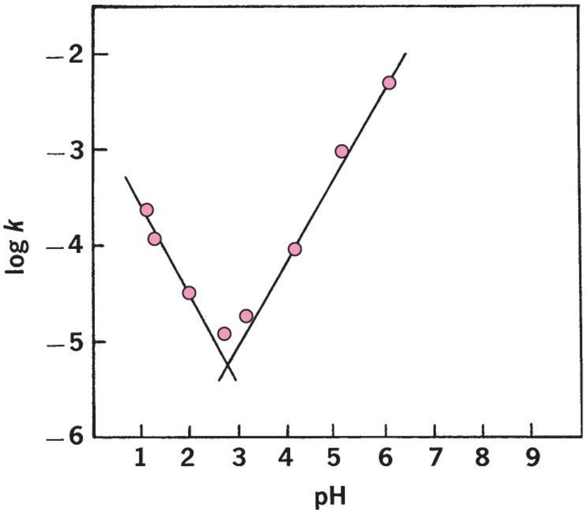
$$dP/dt = k_0[A]$$

Where

$$k_{obs} = k_0$$

- In some cases a minimum plateau that extends over a pH region exists instead of a minimum point.

3.14. Specific Acid – Base Catalysis:



3.14. Specific Acid – Base Catalysis:

- Solvent catalysis occurs simultaneously with specific acid or specific base catalysis.
- The pH dependency of a specific acid-base-catalyzed reaction may be summarized as:

$$dP/dt=k_0[A] + k_1[H^+][A] + k_2[OH^-][A]$$

$$dP/dt=(k_0 + k_1[H^+] + k_2[OH^-])[A]$$

$$dP/dt=k_{obs}[A]$$

Where

$$k_{obs}=k_0 + k_1[H^+] + k_2[OH^-]$$

3.14. Specific Acid – Base Catalysis:

Example 14-12: Martin's 6th ed.:

A sample of glucose was decomposed at 140°C in a solution containing 0.03M HCl. The velocity constant, k, was found to be 0.008 hr^{-1}. If the spontaneous rate constant, k_0, is 0.001 hr^{-1}, compute <u>the catalytic coefficient, k_H.</u>

$$\boldsymbol{k_{obs} = k_0 + k_H[H^+] + k_{OH}[OH^-]}$$

$$\boldsymbol{0.008= 0.001 + k_H \times 0.03}$$

$$\boldsymbol{k_H= 0.007/0.03 = 0.233\ M^{-1}\ hr^{-1}}$$

3.16. Modes of Pharmaceutical Degradation

- Hydrolysis
  - Hydrolysis of esters and amides is the most common example, these reactions are dependent on H^+ and OH^- ions as catalysts so in order to stabilize the formulation, the pH must be adjusted to match the minima in the stability-pH profile if possible.

- Oxidation
  - Can be prevented by a variety of approaches including the manufacturing and packaging under inert conditions, addition of antioxidants (ascorbic acid, Na sulphite, metabisulphite and bisulphate), the use of chelating agents, reduction in storage temperature and formulation at optimum pH for stability.

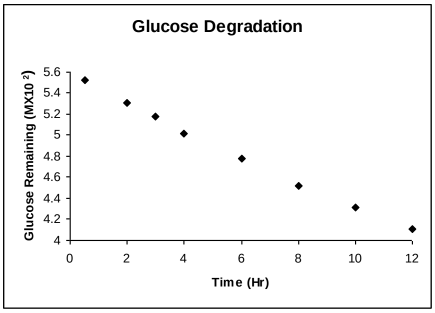
3.16. Modes of Pharmaceutical Degradation

- Photolysis
  - Light energy can provide the necessary activation energy for the reaction to occur.
  - Radiations of sufficient energy and proper frequency must be absorbed to activate drug molecule to undergo reactions.
  - Photochemical reactions do not depend on temperature to activate the molecules.
  - However, the initial photochemical reactions may be followed by thermal reactions.
  - Ergosterol conversion to Vit. D is an example of a biological photochemical reaction (photosynthesis).
  - Light effect is not considered a type of catalysis.
  - Furosemide and Nifedipine are examples of drug undergoing photodegradation.

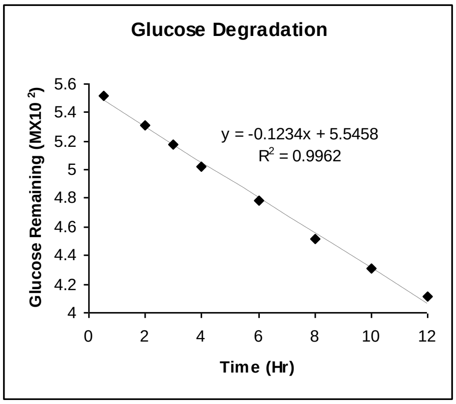
Examples (1):

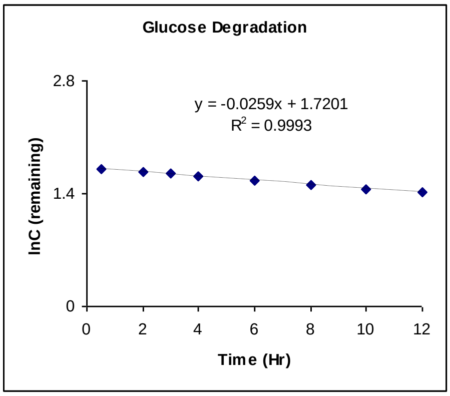
- Degradation of glucose in 0.35 N HCl:

Time (Hr)	Glucose Remaining ($MX10^2$)
0.5	***5.52***
2	***5.31***
3	***5.18***
4	***5.02***
6	***4.78***
8	***4.52***
10	***4.31***
12	***4.11***



Examples (1):





Examples (1):

$\ln C = \ln C_0 - kt$

- Slope = -k = - 0.0259
- K=0.0259
- Half life = 0.693/k= 0.693/0.0259=26.8 hr
- The data has been collected for less than one half life, to get the best estimate of reaction order and half life, the data should be collected over 2 or 3 half lives.

Examples (2):

- The *first-order rate constant* for the decomposition of ampicillin at pH 5.8 and 35°C is $k_1 = 2x10^{-7}\ sec^{-1}$. The *solubility* of ampicillin is *1.1 g/100 ml*. If it is desired to prepare a suspension of the drug containing *2.5g/100ml*, calculate:

  1.The zero order rate constant:

  - The reaction is a pseudo zero order rate reaction, the rate constant of a zero order rate is equal to the rate.
  - The constant rate of decomposition is:

$$2x10^{-7}\ sec^{-1} x1.1g/100ml = 2.2x10^{-7}\ gm/100ml.sec$$

Examples (2):

2. The shelf life at 35°C:

The zero order rate equation is

$$A_t=A_0-k_0t$$

The shelf life is the time required for 10% of ampicillin to degrade:

By the shelf life $t_{0.9}$, $A_t=A_{0.9}=0.9A_0$

$$0.9A_0=A_0-k_0t$$
$$0.1A_0=k_0t_{0.9}$$
$$0.1(2.5g/100ml)= 2.2x10^{-7}\ g/100ml.sec\ (t_{0.9})$$
$$(t_{0.9})=1.14x10^{6}\ sec = 13.2\ days$$

Examples (2):

3. If the drug is formulated in solution rather than a suspension at this pH and temperature, what is the shelf life?

Solution degradation kinetic is first order, the shelf life is:

$$logC = logC_0 - kt/2.303$$
$$log0.9C_0=logC_0-kt_{0.9}/2.303$$
$$log0.9C_0 – logC_0= - kt_{0.9}/2.303$$
$$log(C_0/0.9C_0)=kt_{0.9}/2.303$$

$$log\ (1/0.9)=kt_{0.9}/2.303$$
$$0.0458=kt_{0.9}/2.303$$
$$0.105= (2x10^{-7})\ t_{0.9}$$
$$t_{0.9} = 5.27x10^{5}\ sec$$

Examples(3):

- The photodegradation of Menadione is a first order reaction with a rate constant $k=4.863x10^{-3}min^{-1}$.

  1. Calculate the half life of menadione:

  $T_{0.5}=0.693/4.863x10^{-3}min^{-1}=142.5$ *minutes*

Examples (3):

- Menadione is stabilized by a quaternary ammonium compound.
- The data for the photolysis of $5.19x10^{-5}M$ of menadione solution containing 5% w/w stabilizer is as follows:

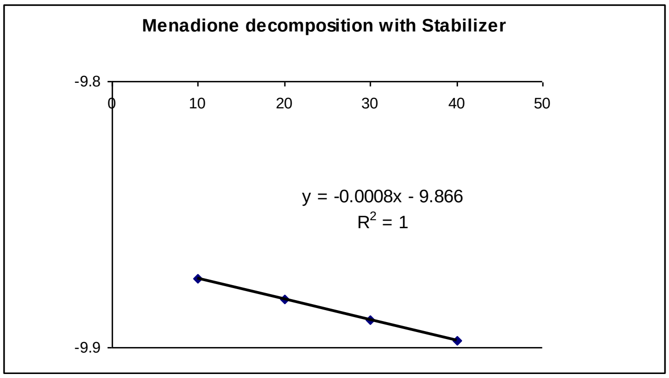
Time (min)	**10**	**20**	**30**	**40**
Menadione Remaining	**$5.15x10^{-5}$**	**$5.11x10^{-5}$**	**$5.07x10^{-5}$**	**$5.03x10^{-5}$**

Examples (3):

2. Calculate k and $t_{0.5}$:

Time (min)	**10**	**20**	**30**	**40**
Menadione Remaining (M)	**$5.15x10^{-5}$**	**$5.11x10^{-5}$**	**$5.07x10^{-5}$**	**$5.03x10^{-5}$**
ln C	**-9.8739**	**-9.8817**	**-9.8896**	**-0.8975**

Examples (3):



Examples (3):

- From the graph, $k = 0.0008\ min^{-1}$
- $T_{0.5}$= $0.693/0.0008=866$ *minutes*
- *What is the concentration after 5 hours with or without a complexing agent?*

Using the first order equation

$$lnC=lnC_0-kt$$

Without a complexing agent

$$lnC_{5\ hours}=ln5.19x10^{-5}-(4.863x10^{-3}min^{-1})(5x60\ min)$$
$$lnC_{5\ hours}=-9.87-1.46$$
$$lnC_{5\ hours}=-11.33$$
$$C_{5\ hours}=1.2x10^{-5}\ M$$

Examples (3):

With a complexing agent

$$lnC_{5\ hours}=ln5.15x10^{-5}-(0.0008\ min^{-1})(5x60\ min)$$

$$lnC_{5\ hours}=-9.87-0.24$$

$$lnC_{5\ hours}=-10.11$$

$$C_{5\ hours}=4.07x10^{-5}\ M$$

Examples (4):

- The decomposition reaction of a new drug molecule was found to be first order. The initial concentration *C_0* of the solution was *0.050 M* and after *10 hours* at *40°C*, the drug concentration *C* was *0.015 M*.
  - Compute the specific rate constant at 40°C
  - What is the drug concentration after 2 hours
  - If the k value for this reaction at 20°C is 0.0020 hr^{-1}, what is the activation energy and the Arrhenius factor of the reaction?

Examples (4):

Rate Constant at 40°C

$$\ln C=\ln C_0-kt$$

$$\ln C_{10}=\ln C_0-k(10)$$

$$\ln(0.015)=\ln(0.05)-10k$$

$$-4.19=-2.99-10k$$

$$-1.2=-10k$$

$$K=0.12\ hr^{-1}$$

Examples (4):

- Concentration after 2 hours ($C_{2\ Hr}$):

$$lnC=lnC_0-kt$$
$$lnC_2=lnC_0-k(2)$$
$$lnC_2=ln(0.05)-(0.12)(2)$$
$$lnC_2= -2.99 – 0.24$$
$$lnC_2=-3.23$$

$$C_2=0.039\ M$$

Examples (4):

- The activation energy and Arrhenius constant can be calculated using the Arrhenius equation for the two temperatures (40^oC & 20^oC).

$$ln(k)=lnA – E_a/RT$$

- You can prepare two equation and solve for the two unknowns (A &E_a):

$$For\ 20^oC$$
$$ln(0.002) = lnA – E_a/(1.9872)(293.15)$$
$$ln(0.002) = lnA – E_a/(582.55)$$
$$ln(0.002)= lnA – E_a/(582.55)$$
$$-6.21= lnA – E_a/(582.55)$$
$$lnA = - 6.21 + E_a/(582.55)$$

Examples (4):

For 40^{o}C

$\ln(0.12) = \ln A – E_a/(1.9872)(313.15)$

$\ln(0.12) = \ln A – E_a/(622.29)$

$\ln(0.12)= \ln A – E_a/(622.29)$

$- 2.12= \ln A – E_a/(622.29)$

From the 20^{o}C Data we know that

$\ln A = - 6.21 + E_a/(582.55)$

So

$- 2.12= - 6.21 + E_a(0.00172) – E_a(0.00161)$

$- 2.12 = - 6.21 + E_a(0.00011)$

$E_a= 4.09/(0.00011)$

$E_a= 37181.82$ cal/mol

Examples (4):

- The Arrhenius factor is calculated from:

$$\ln A = - 6.21 + E_a/(582.55)$$

$$\ln A = -6.21 + 37181.82/(582.55)$$

$$\ln A = - 6.21 + 63.82$$

$$\ln A = 57.61$$

$$A=1.05\times 10^{25} /Hr$$

Examples (5):

- The degradation of *Phentolamine HCl* in *phosphate buffer* at *pH 5.9 to 7.2* and 90°C is attributed to the *specific base catalysis.* The value of the specific base catalysis constant K_{OH} was found to be $4.28 \times 10^{6}\ l.mol^{-1}.hr^{-1}$. The solvent effect is negligible $k_0 = 0$.
- Write the overall rate equation and rate constant:

$Rate = k_{OH}[OH^-][Drug]$

$k_{obs} = k_{OH}[OH^-]$

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Examples (5):

- Compute the overall hydrolysis rate constant *k* at the *pH* value of *6*

We firstly calculate the $[OH^-]$:

at pH=6

$-\log[H^+]=6$

$\log[H^+]=-6$

$[H^+]= 1 \times 10^{-6}$

As we know

$[H^+][OH^-]=kw=10^{-14}$

$1 \times 10^{-6}[OH^-]=10^{-14}$

$[OH^-]=10^{-8}$

$k_{obs} = k_{OH}[OH^-]$

$k_{obs} = (4.28 \times 10^{6})(10^{-8})$

$k_{obs} = 4.28 \times 10^{-2}\ hr^{-1}$

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