Kinetics

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Kinetics

Kinetics

- The study of the rate of chemical change and the way this rate is influenced by conditions of concentration of reactants, products, and other chemical species that may be present and by factors such as solvent, pressure, and temperature

Importance of Kinetics

1. Selection of proper storage temperature, light and advising patient on storage conditions
2. Selection of proper container for dispensing
   - Glass vs. plastic
   - Clear vs. amber vs. opaque
3. Anticipation of interactions when mixing drugs and dosage forms (incompatibilities)
   - Active drugs
   - Excipients
4. Dissolution determinations

Importance of Kinetics (cont'd)

5. ADME Processes in pharmacokinetics

A = Absorption

D = Distribution

M = Metabolism/Biotransformation

E = Excretion

6. Drug action at the molecular level

7. Dispense oldest stock first and observe expiration dates.
8. Store products under conditions stated in USP monographs and/or labeling.
9. Observe products for evidence of instability.
10. Properly treat/label products that are repackaged, diluted, or mixed with other products.

Reaction Mechanisms

Rate Laws for Elementary Steps

TABLE 14.3 Elementary Steps and Their Rate Laws

Molecularity	Elementary Step	Rate Law
*Uni*molecular	$A \longrightarrow$ products	Rate $= k[A]$
*Bi*molecular	$A + A \longrightarrow$ products	Rate $= k[A]^2$
*Bi*molecular	$A + B \longrightarrow$ products	Rate $= k[A][B]$
*Ter*molecular	$A + A + A \longrightarrow$ products	Rate $= k[A]^3$
*Ter*molecular	$A + A + B \longrightarrow$ products	Rate $= k[A]^2[B]$
*Ter*molecular	$A + B + C \longrightarrow$ products	Rate $= k[A][B][C]$

Rate of the reaction

Expressing speed of a reaction:

- as the decrease in concentration of any reacting substance
- as the increase in concentration of the product per unit time.

- If C is the concentration, then the rate of reaction:

$$\frac{dC}{dt} \alpha C^{n}$$

- where n=0,1 or 2 for zero, first & second order reactions respectively

- Manner in which the rate of reaction varies with the concentration of the reactants
- Most processes involving ADME can be treated as first- order processes
- Some drug degradation processes can be treated as either First or zero order processes
- Some drug substances obey Michaelis-Menten kinetic process

- n=1 and the reaction rate is dependent on the concentration of one of the reactants in the formulation.
- $$-\frac{dC}{dt} = kC$$
- C is the concentration remaining un-decomposed, unabsorbed, yet to be distributed, metabolized or excreted at time t as the case may be
- k is the first order rate constant.

First-Order Reactions

$$C \longrightarrow \text{product}$$

Rate constant

$$k = \frac{\text{rate}}{[C]} = \frac{M/s}{M} = s^{-1}$$

Average rate

$$\text{rate} = -\frac{\Delta[C]}{\Delta t}$$

Rate law

$$\text{rate} = k[C]$$

Differential rate law

$$-\frac{\Delta[C]}{\Delta t} = k[C]$$

Integrated rate law

$$[C] = [C]_0 \exp(-kt)$$

Integrated rate law (linear form)

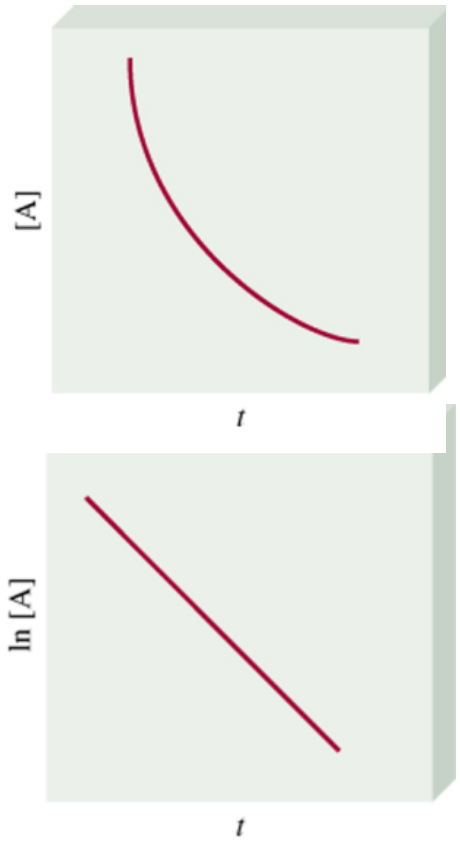
$$\ln[C] = \ln[C]_0 - kt$$

[A] is the concentration of A at any time t

$[A]_0$ is the concentration of A at time t=0

First-Order Reactions

C ⟶ product



Average rate $\text{rate} = -\frac{\Delta[C]}{\Delta t}$

Rate law $\text{rate} = k[C]$

Differential rate law $-\frac{\Delta[C]}{\Delta t} = k[C]$

Integrated rate law $[C] = [C]_0 \exp(-kt)$

Integrated rate law (linear form) $\ln[C] = \ln[C]_0 - kt$

[A] is the concentration of A at any time t

$[A]_0$ is the concentration of A at time t=0

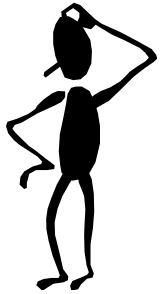
- On integration, the equation above gives:

$$\ln C - \ln C_o = -k(t - 0)$$

- On rearrangement and conversion to log in base 10:

$$\log C = \log C_o - \frac{kt}{2.303}$$


Log
Conc
.
Slope = -k/2.303
Time



The reaction $2C \longrightarrow B$ is first order in A with a rate constant of $2.8 \times 10^{-2}\ s^{-1}$ at 80^0C. How long will it take for A to decrease from 0.88 *M* to 0.14 *M*?

$$\ln[C] = \ln[C]_0 - kt$$

$$[C]_0 = 0.88\ M$$

$$[C] = 0.14\ M$$

$$kt = \ln[C]_0 - \ln[C]$$

$$t = \frac{\ln[C]_0 - \ln[C]}{k} = \frac{\ln \dfrac{[C]_0}{[C]}}{k} = \frac{\ln \dfrac{0.88\ \cancel{M}}{0.14\ \cancel{M}}}{2.8 \times 10^{-2}\ s^{-1}} = 66\ s$$

Recall:

$$\ln x - \ln y = \ln \frac{x}{y}$$

First-Order Reactions

The ***half-life***, $t_{1/2}$, is the time required for the concentration of a reactant to decrease to half of its initial concentration.

$$t_{1/2} = t \text{ when } [C] = [C]_0/2$$

What is the half-life of N_2O_5 if it decomposes with a rate constant of $5.7 \times 10^{-4}\ s^{-1}$?

$$t_{1/2} = \frac{\ln 2}{k} = \frac{0.693}{5.7 \times 10^{-4}\ s^{-1}} = 1200\ s = 20\ \text{minutes}$$

How do you know decomposition is first order? units of k (s^{-1})

The half-life of a 1st-order reaction is independent of the initial concentration of the reactant.

Second-Order Reactions

$C \longrightarrow$ product

$$\text{rate} = -\frac{\Delta[C]}{\Delta t}$$

$$\text{rate} = k[C]^2$$

$$k = \frac{\text{rate}}{[C]^2} = \frac{M/s}{M^2} = 1/M \cdot s$$

$$-\frac{\Delta[C]}{\Delta t} = k[C]^2$$

$$\frac{1}{[C]} = \frac{1}{[C]_0} + kt$$

[A] is the concentration of A at any time t

$[A]_0$ is the concentration of A at time t=0

$t_{1/2} = t$ when $[C] = [C]_0/2$

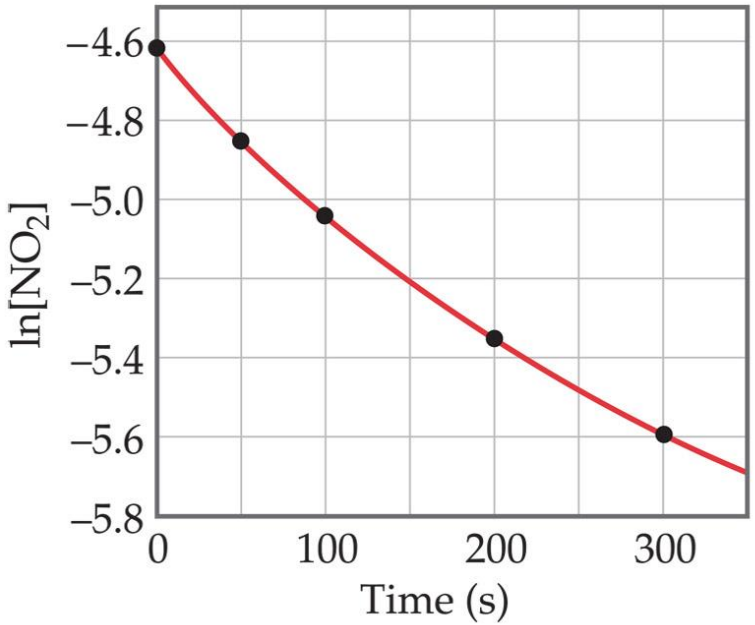
$$t_{1/2} = \frac{1}{k[C]_0}$$

Distinguishing 1st and 2nd order reactions

$NO_{2(g)} \longrightarrow NO_{(g)} + \frac{1}{2} O_{2(g)}$ at 300°C

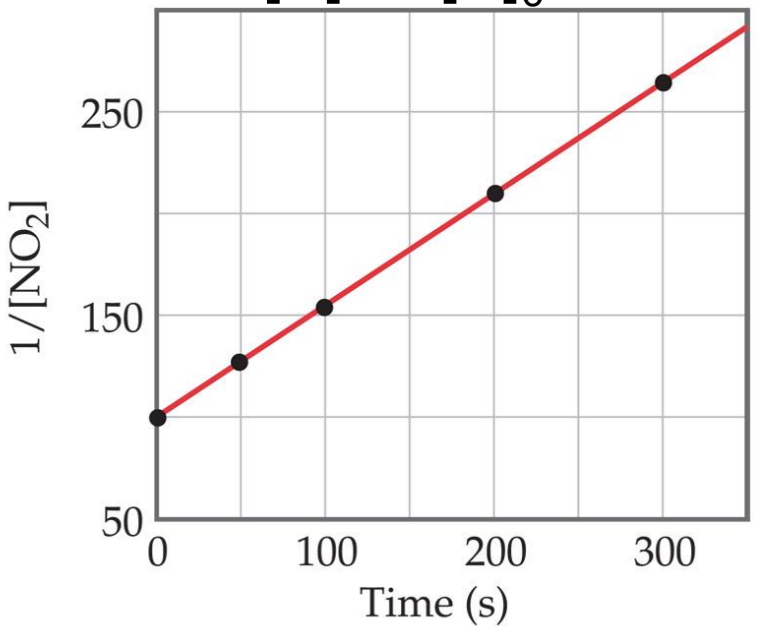
- Is the rate law 1st or 2nd order?
  - If (a) plot gives a straight line, then 1st order and rate = $k[C]$
  - If (b) plot gives a straight line, then 2nd order and rate = $k[C]^2$

$$\ln[C] = \ln[C]_0 - kt$$



(a)

$$\frac{1}{[C]} = \frac{1}{[C]_0} + kt$$



(b)

Zero order kientic

- In this type of reaction, n=0 and the reaction rate is independent of the concentration of the reacting substance.
- The rate of change is constant.
- Here, factors other than concentration of reactants constitute the limiting factor e.g. solubility or absorption of light (photochemical reactions).

Zero-Order Reactions

C $\longrightarrow$ product

$$\text{rate} = -\frac{\Delta[C]}{\Delta t}$$

$$\text{rate} = k[C]^0 = k$$

$$k = \frac{\text{rate}}{[C]^0} = M/s$$

$$-\frac{\Delta[C]}{\Delta t} = k$$

$$[C] = [C]_0 - kt$$

[A] is the concentration of A at any time t

$[A]_0$ is the concentration of A at time t=0

$t_{1/2} = t$ when $[C] = [C]_0/2$

$$t_{1/2} = \frac{[C]_0}{2k}$$

- When solubility is the limiting factor, only the proportion of drug in solution undergoes degradation:
  - *As the drug is consumed in the degradative reaction, more drug goes into solution until all solid (C) has reacted.*
  - *Until this has happened, the degradation process will not be dependent on the total conc. of drug but on the proportion in solution, thereby producing a zero order process*.

- Zero order Equation:

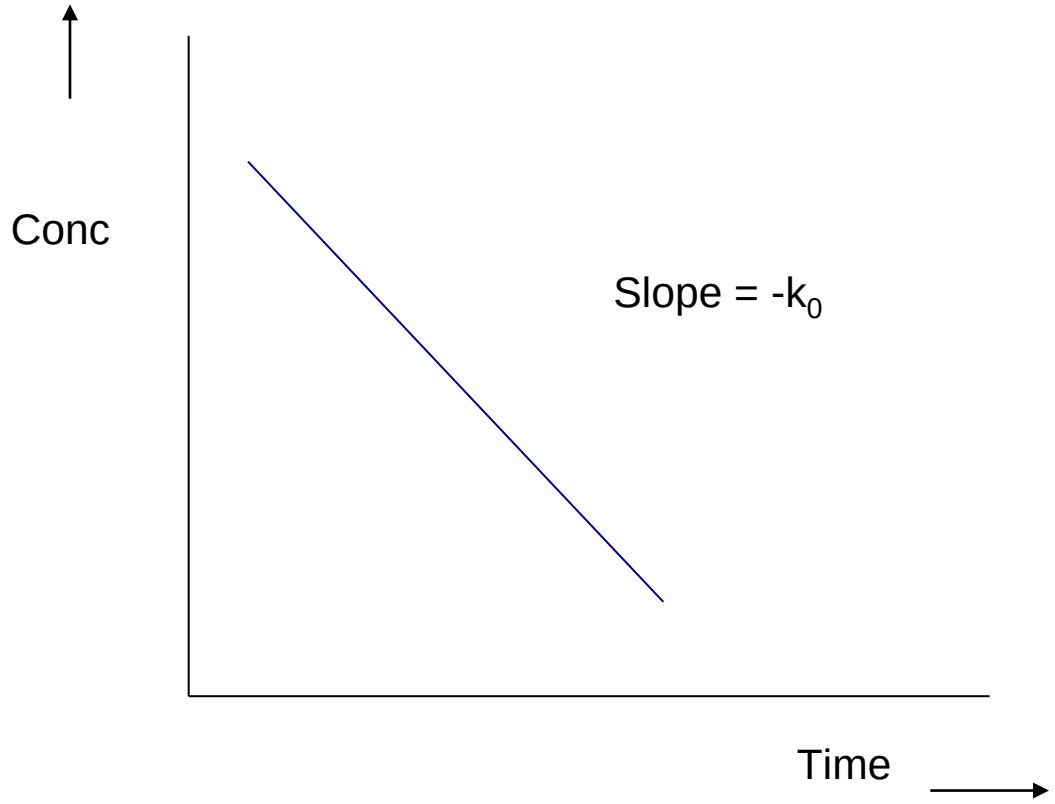
$$\frac{-\,dC_{o}}{dt} = k$$

- C_o= original concentration of reacting material, k=reaction rate constant, dt= change in time.

- Expression of zero order equation:

$$C_t = C_o - kt$$

- C_t=conc. at time t, C_o=conc. at time o.
- Plot of C against t gives a straight line with slope of $-k_o$


Conc
Slope = -k_0
Time

- For a zero order reaction, the time for 50% reaction, $t_{1/2}$, is given as:

$$t_{1/2} = \frac{\frac{1}{2}C_o}{k_o} = \frac{C_o}{2k_o}$$

- Suspensions are a special case of zero order kinetics, in which the concentration of drug in solution depends on its solubility.
- As the drug in solution decomposes, more of it is released from a reservoir of suspended particles thereby making the concentration in solution constant.
- The effective concentration is the drug equilibrium solubility in the solvent of formulation at given temperatures

- Ordinarily, the equation for decomposition is first order:

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

- C=the conc. of drug remaining un-decomposed at time t
- k=the known first order rate constant.

- When concentration is rendered constant by suspended particles offering replacement, then

$$k\left[C\right] = k_o$$

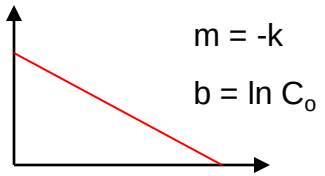
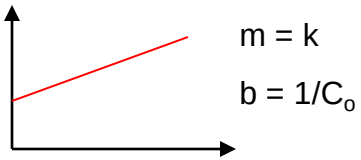
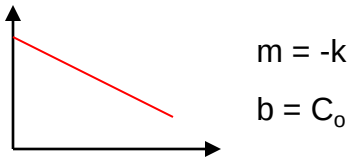
- thereby turning the first order rate law into;
-

$$\frac{-d\left[C\right]}{dt} = k_o$$

- Can present as;
  - Loss of potency
  - Accumulation of toxic degradative products
  - Degrardation of excipient responsible for product stability e.g. emulsifying agents, preservatives
  - Conspicuous colour change e.g. marked discoloration of adrenaline although very slight change in adrenaline content, is unacceptable to patients, pharmacists, physicians and the nurses.

- Generally, chemical reactions proceed more readily in liquid state than in solid state
- Serious stability problems are more commonly encountered in liquid medicines e.g. order of dosage form stability is generally: solution < suspension < tablet.

Summary of Rate Laws to One-Component

	First-Order	Second-Order	Zeroth-Order
differential rate law (-dC/dt)	kC	kC^2	k
Equation	$C = C_o \cdot e^{-kt}$ $\ln C = -kt + \ln C_o$	$1/C = kt + 1/C_o$	$C = -kt + C_o$
Linear Equation	ln C vs. t	1/C vs. t	C vs. t
Linear Plot			
Half-Life	$\ln(2)/k$	$1/kC_o$	$C_o/2k$
Units on k	$time^{-1}$	$M^{-1}\ time^{-1}$	$M\ time^{-1}$

Determination of Order of Reaction

- Use of rate equation – The data collected in a kinetic reaction should be substituted into the integrated form of equations of various orders.
  - The process under test should be considered to be of that order where the calculated k value remains constant within limits of experimental error.

Determination of Order of Reaction..

- Half life method – For a zero order or pseudo first order reaction, t ½ is proportional to initial concentration of reactant (Co),
  - t½ for a first order reaction is independent of Co, .
- Graphical method – For a zero order or pseudo first order reaction, plot of C vs. t is linear; for first order reaction, plot of log (Co-Ct) vs. t is linear.

Factors Affecting Rate of Reactions

- The rate of reaction (degradation of pharmaceutical products) can be influenced
  - temperature,
  - moisture,
  - solvent (pH, dielectric constant, etc),
  - light (radiation),
  - catalysts,
  - oxygen and
  - concentration of reactant (s).

Temperature

- Temperature – Rate of most chemical reactions increase with rise in temperature up to 2 to 3 times with each 10° rise in temperature.
- The relationship is expressed by Arrhenius equation:

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

Arrhenius equation

- Log transformation gives:

$$\log\ k = \log\ A - \frac{E_a}{2.303}\frac{1}{RT}$$

- k is the rate of reaction
- A is a constant known as the frequency factor E_a is the activation energy,
- R is the gas constant (1.987 calories $deg^{-1} mole^{-1}$ OR 8.314 J $mole^{-1}$)
- T is the absolute temperature.

- Plot of log k against 1/T gives a straight line with slope of –Ea/2.303R and intercept of log A.
- For a reaction carried out at 2 diff. temp., (subtracting eqn. 1 from 2 gives:

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

- The time required for 10 % of the drug to degrade with 90 % of intact drug remaining is based on Arrhenius equation:

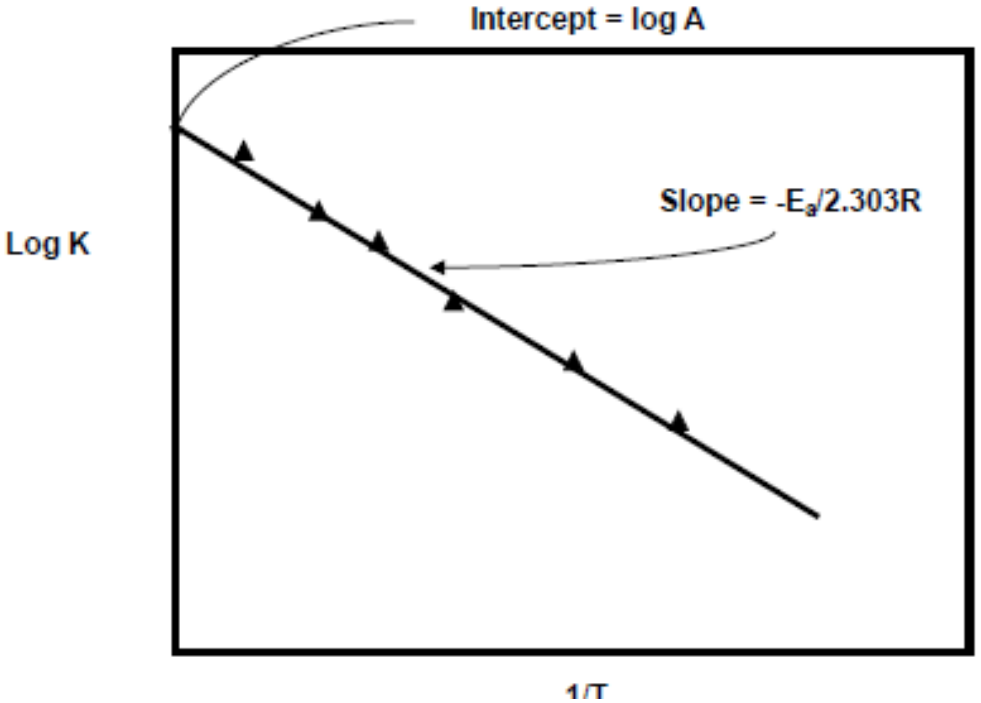
$$\log \frac{k_2}{k_1} = \frac{E_a (T_2 - T_1)}{2.303 \; RT_1 T_2}$$

- k = reaction rate, T = temperature,
- R = gas constant, Ea = activation energy

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 I

How to determine A and E_a? Cont.

2. The best estimation of the Arrhenius constant and ac
energy is obtained by performing the reaction at three d
temperatures at least (log k vs. 1/T). However two temp
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 Ra

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

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

*Log (4.86/1.173)= [Ea/(2.303*1.987)]*[(413-393)/413*39*

Ea= 22,926 cal/mol= 22.9 kcal/mol

B. Compute A:

At 120°C:

$$\log k_1 = \log A - \frac{\mathrm{Ea}}{2.303\mathrm{RT}_1}$$

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!

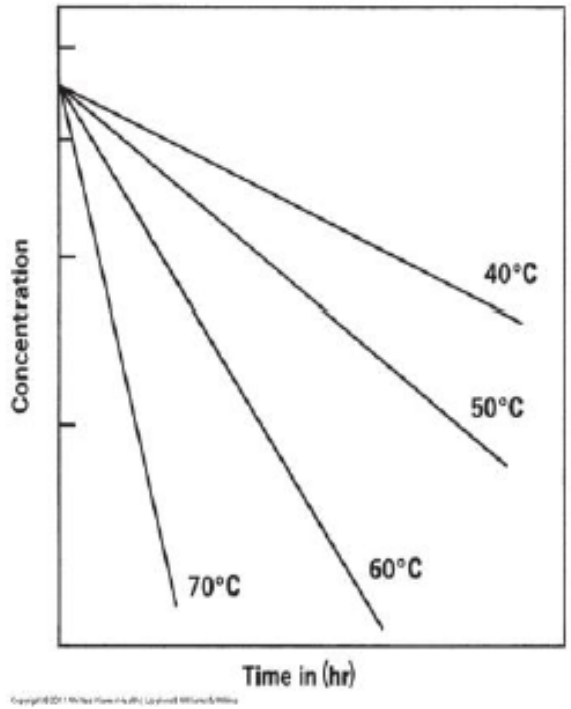
Compare that to the shelf life at 25°C? (3.75 days)

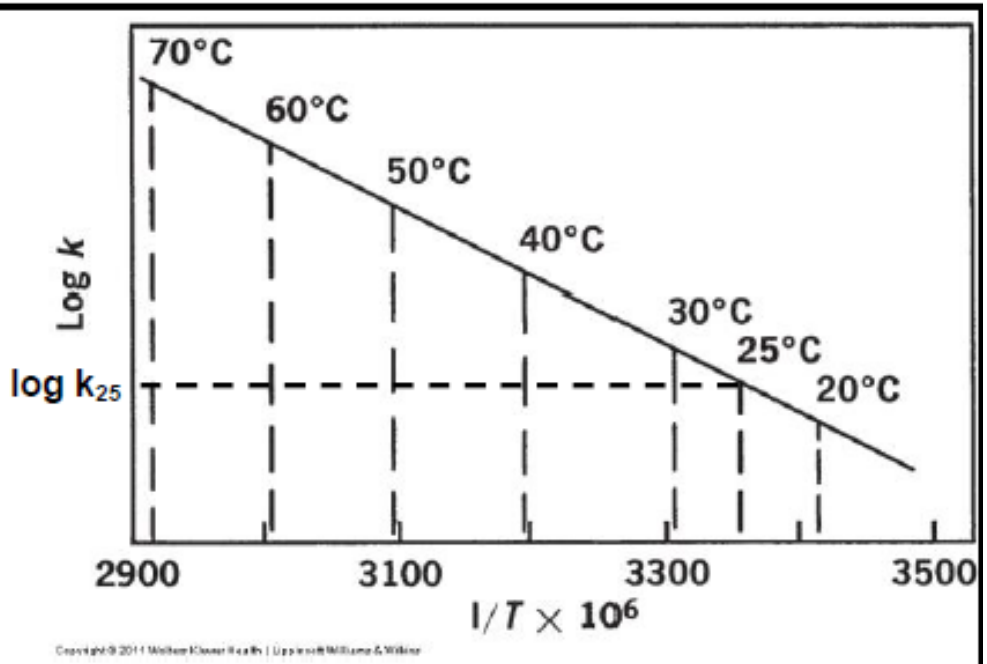
Accelerated Stability Testing:

- 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.





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)

Physical Paths of Instability

- 1. Polymorphs
  - Cocoa butter, Cortisone Acetate
- 2. Crystallization
  - Solutions, suspensions
- 3. Vaporization
  - Flavoring agents, cosolvents, nitroglycerin
- 4. Particle sedimentation
  - Suspensions

Reaction Kinetics

- Want two things from kinetic data:
  - Reaction order
  - Reaction rate
- In considering the chemical stability of a pharmaceutical, we need to know the REACTION ORDER, which is obtained experimentally by measuring the REACTION RATE as a function of concentration of the degrading drug.

Chemical Kinetics vs. Chemical Stability

- **KINETICS**
- Several half-lives
- Pure systems
- Goal is to elucidate reaction mechanisms.

- **STABILITY**
- Down to about 85% of drug remaining
- Involves complete dosage form
- Goal is to establish an expiration date.