Chemical Kinetics and Stability

Introduction

Basic requirements of pharmaceutical products

- **Efficacy: Optimum therapeutic level for specified period of time.**
- **Safety: Minimum or no side effects.**
- **Stability: The products should retain their properties during storage.**

Physical Chemical

This should guarantee the efficacy and safety

The purpose of stability testing is:

- **to provide evidence on 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,**

- **and to establish a shelf life for the drug product and recommended storage conditions.**

Chemical reaction rate

The study of rate of chemical degradation in which the rate is influences by solvent , pressure ,and temperature of the product and reactants

Reaction order are generally classified into :

- **Zero order reaction**
- **First order reaction**
- **Second order reaction**
- **Third order reaction**
- **Pseudo first order reaction**

Rates, Order, and Molecularity of Reactions

- The rate, velocity, or speed of a drug degradation reaction is given by the expression *dc/dt*,
- where *dc* is the increase or decrease of concentration over an infinitesimal time interval *dt*.

Zero 1st 2nd

- The order of the reaction is the manner by which the concentration affects the rate of the reaction.

Rate Constants, Half-Life, Shelf Life, and Apparent or Pseudo-order

- Specific Rate Constant:
- The Rate constant, k,

- Any change in the conditions of the reaction, for example, in temperature or solvent, or a slight change in one of the reacting species, will lead to a rate law having a different value for the specific rate constant.

- The *half-life* is the time required for one-half of the material to disappear; it is the time at which *A (amount of the drug)* has decreased to ½ A_o. ← initial concentration

- The shelf life is the time required for 10% of the material to disappear; it is the time at which *A* has decreased to 90% of its original concentration (i.e., 0.9 A_o.).

Units of the Basic Rate Constants

for a zero-order reaction:

$$k = \frac{\text{moles}}{\text{liter second}} = \text{moles liter}^{-1}\,\text{second}^{-1}$$

for a first-order reaction,

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

for a second-order reaction

$$k = \frac{\text{liter}}{\text{moles-second}} = \text{liter second}^{-1}\,\text{mole}^{-1}$$

zero-order reaction

In this type of reaction the rate of the reaction is independent of the concentration of reactants , the rate of reaction expressed by :

$$dc/dt = K_0$$ ← Rate of reaction is constant

$$A_t = A_0 - k_0 t$$

$$t^{1/2} = C^0 / 2\,k_0$$

$$t_{1/2} = \frac{\frac{1}{2}A_0}{k_0}$$

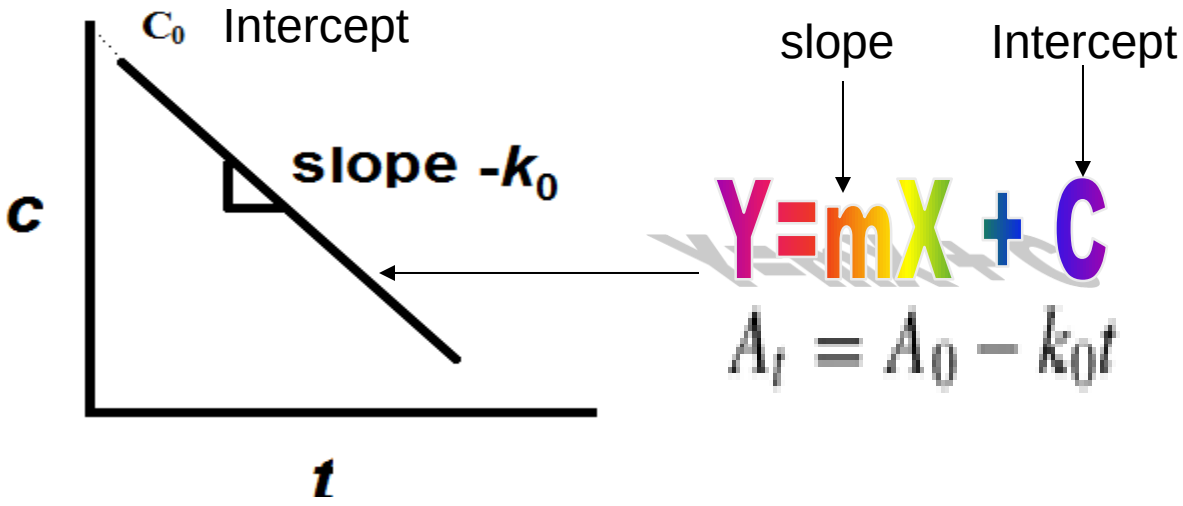
- At or ct = remaining **concentration of reactants**
- **k= constant reaction rate**
- **t= time**
- **A^0 or C^0= initial concentration of reactants**
- **$t^{1/2}$ = half life**

•Example :

Most of photochemical degradations are classified as zero order kinetic

- The initial concentration corresponding to A_0 is ordinarily written as *a* and the concentration remaining at time *t* as *c*.

- When this linear equation is plotted with ***c*** on the vertical axis against ***t*** on the horizontal axis, the slope of the line is equal to $-k_0$.



zero-order reaction

- Because the *half-life* is the time required for one-half of *the material to disappear*, *then:*
- $$t_{1/2} = \frac{\frac{1}{2}A_0}{k_0} \longrightarrow$$ ***t ½= Ao/ 2Ko***
- *The shelf life is (0.1A°./ K°).*

- Example:
- A prescription for a liquid aspirin preparation is called for. It is to contain 325 mg/5 mL or 6.5 g/100 mL. Determine the shelf life a liquid aspirin preparation, assuming that the at 25°C

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

zero-order reaction

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

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

first-order reaction

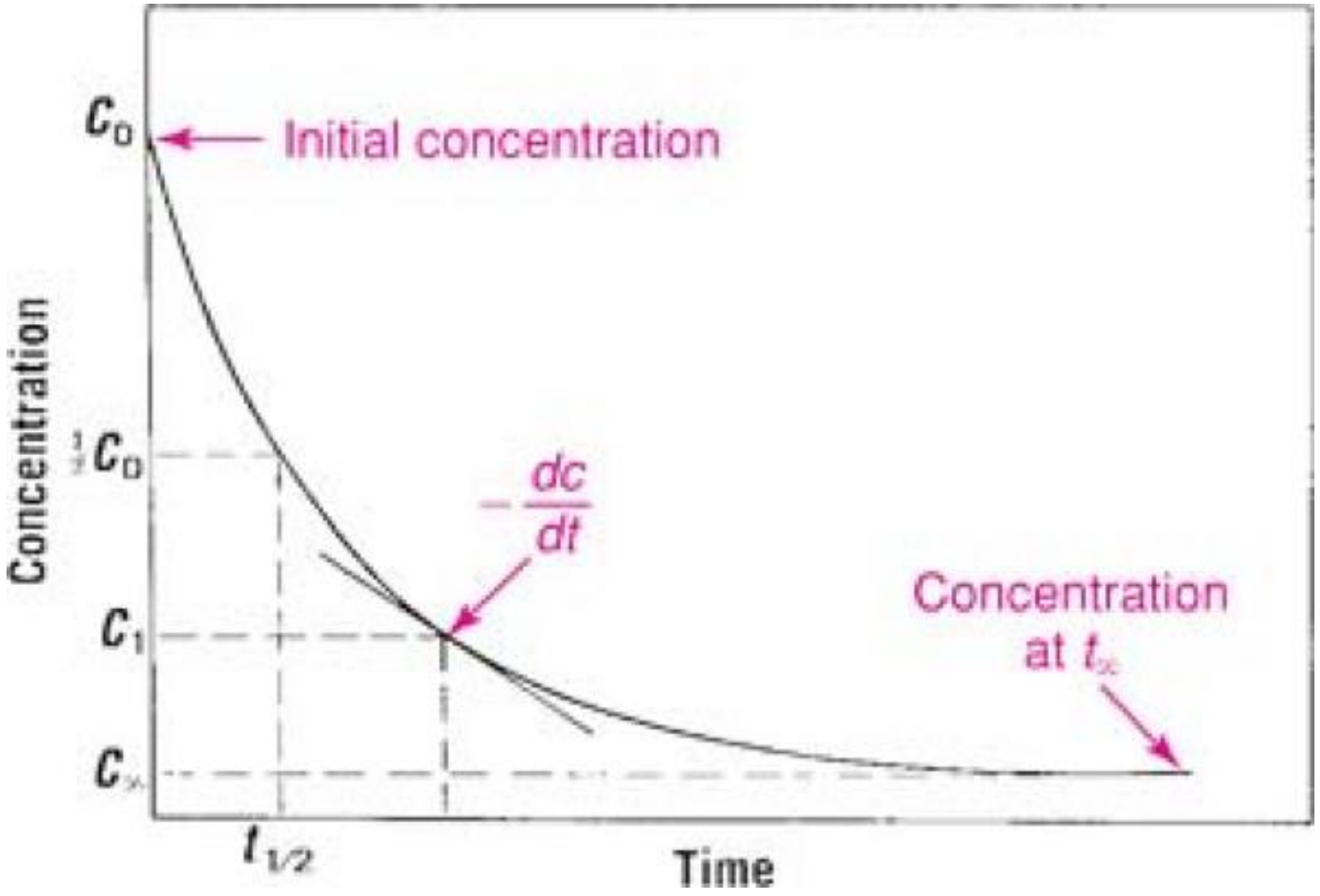
- **When the <u>rate of the reaction</u> is proportional to the first power of concentration of the reactant**
- **Log C_t = Log C_0 – Kt/ 2.303**
- **K = 2.203/t X Log C_0 / C_t**
- **$t^{1/2}$ = 0.693 /K**

- **C_t =** concentration remaining at time *t*
- **C_0 =** initial concentration
- K= reaction rate constant
- **$t^{1/2}$ = half life**

- to obtain an average *k* for the reaction is to plot the logarithm of the concentration against the time.

- The linear expression in equation **(**14-13**)** shows that the slope of the line is -*k*/2.303, from which the rate constant is obtained.

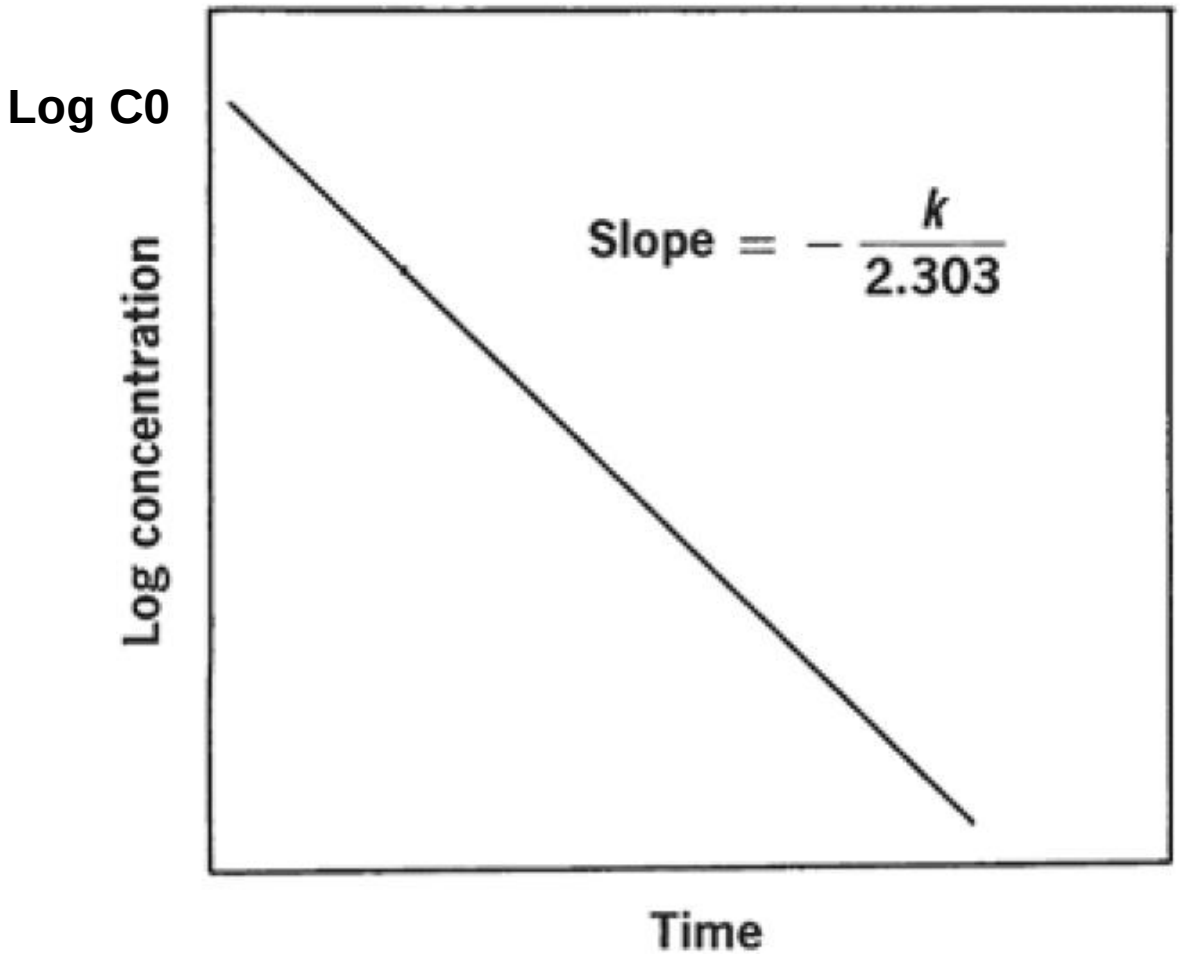
- If a straight line is obtained, it indicates that the reaction is first order.


C_0
Initial concentration
$\frac{1}{2}C_0$
$-\frac{dc}{dt}$
C_1
Concentration at t_∞
C_∞
$t_{1/2}$
Concentration
Time

intercept slope

$$\text{Log } Ct = \text{Log } C0 - Kt/2.303$$

$$Y = mX + C$$



Example:

- 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?**

- **$K = 2.203/t \times \text{Log } C_0 / C_t$**

- **K = 2.203/ 40 day X Log 500 / 300**

  = 0.013 day -1

- **$t^{1/2} = 0.693 / K$**

  = 0.693/ 0.013 **day -1**

  = 54.2 day

- **$K = 2.203/t \ X \ Log \ C_0 / C_t$**

- **K = 2.203/ 57600 sec X Log 500 / 300**

  = 1.48 x10 $^{-7}$ **sec -1**

- **$t^{1/2} = 0.693 /K$**

  = 0.693/ 1.48 x10 $^{-7}$ **sec -1**

  = 468 x10 ^{4} **sec**

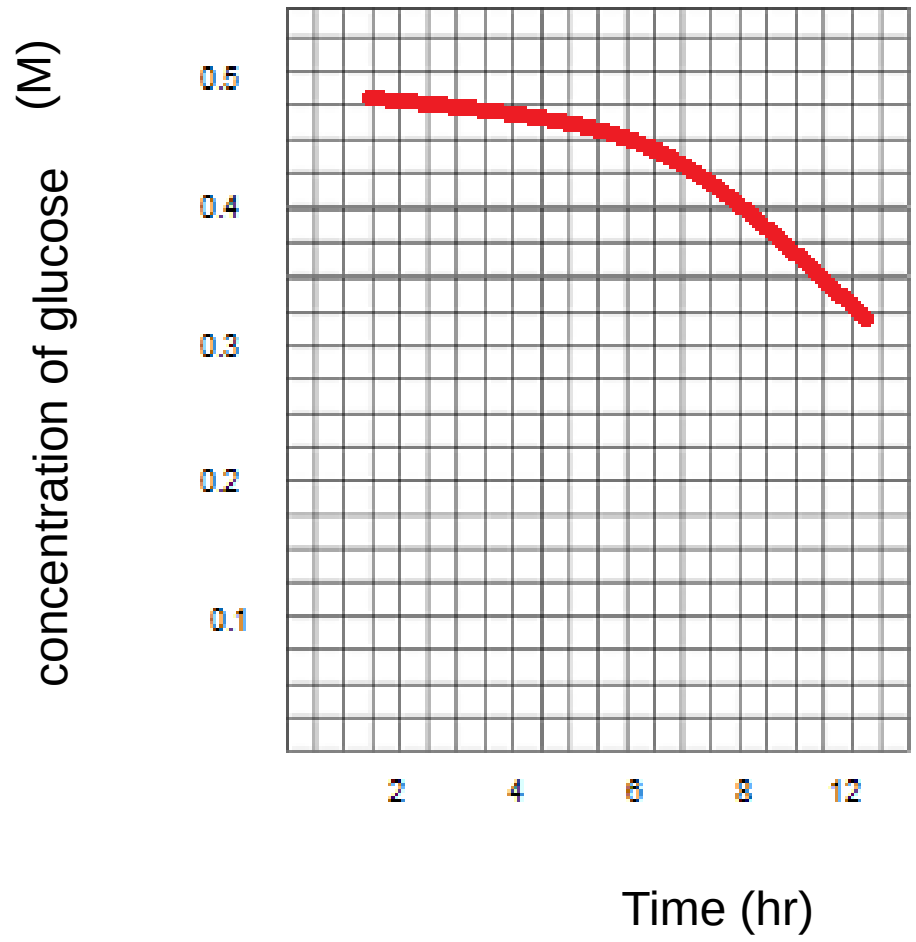
  = 54.2 day

Example:

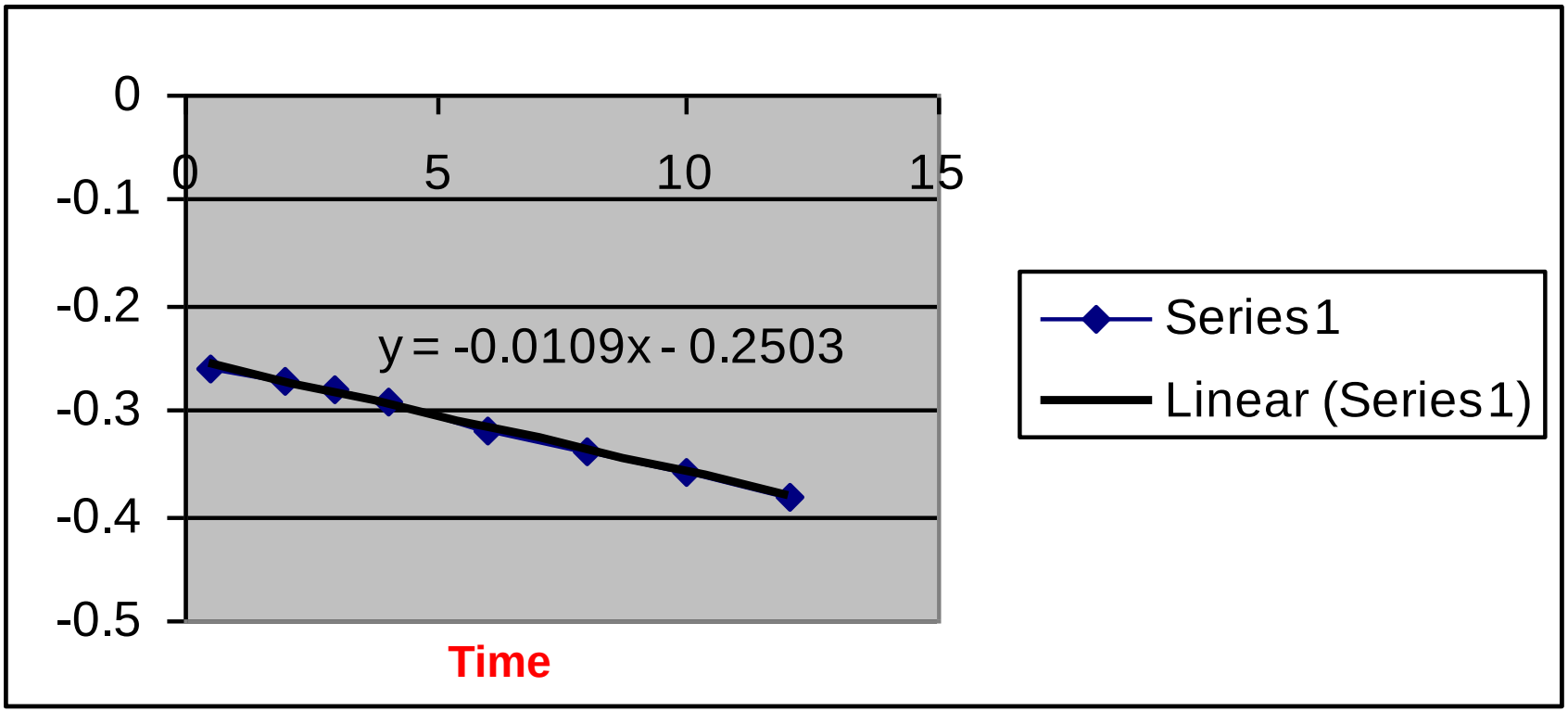
- The time and amount of decomposition of glucose at 40 °C in an aqueous solution of 0.35 N HCl was found to be: (Table)

- What is the order, half life, reaction rate constant, initial concentration of glucose
- What is the remaining concentration after 16 hours.
- How long does it take for decomposition of 0.4 M of glucose.

Time (hr)	Glucose, remaining (M)
0.5	0.552
2	0.531
3	0.518
4	0.502
6	0.478
8	0.452
10	0.431
12	0.411


concentration of glucose (M)
0.5
0.4
0.3
0.2
0.1
2
4
6
8
12
Time (hr)

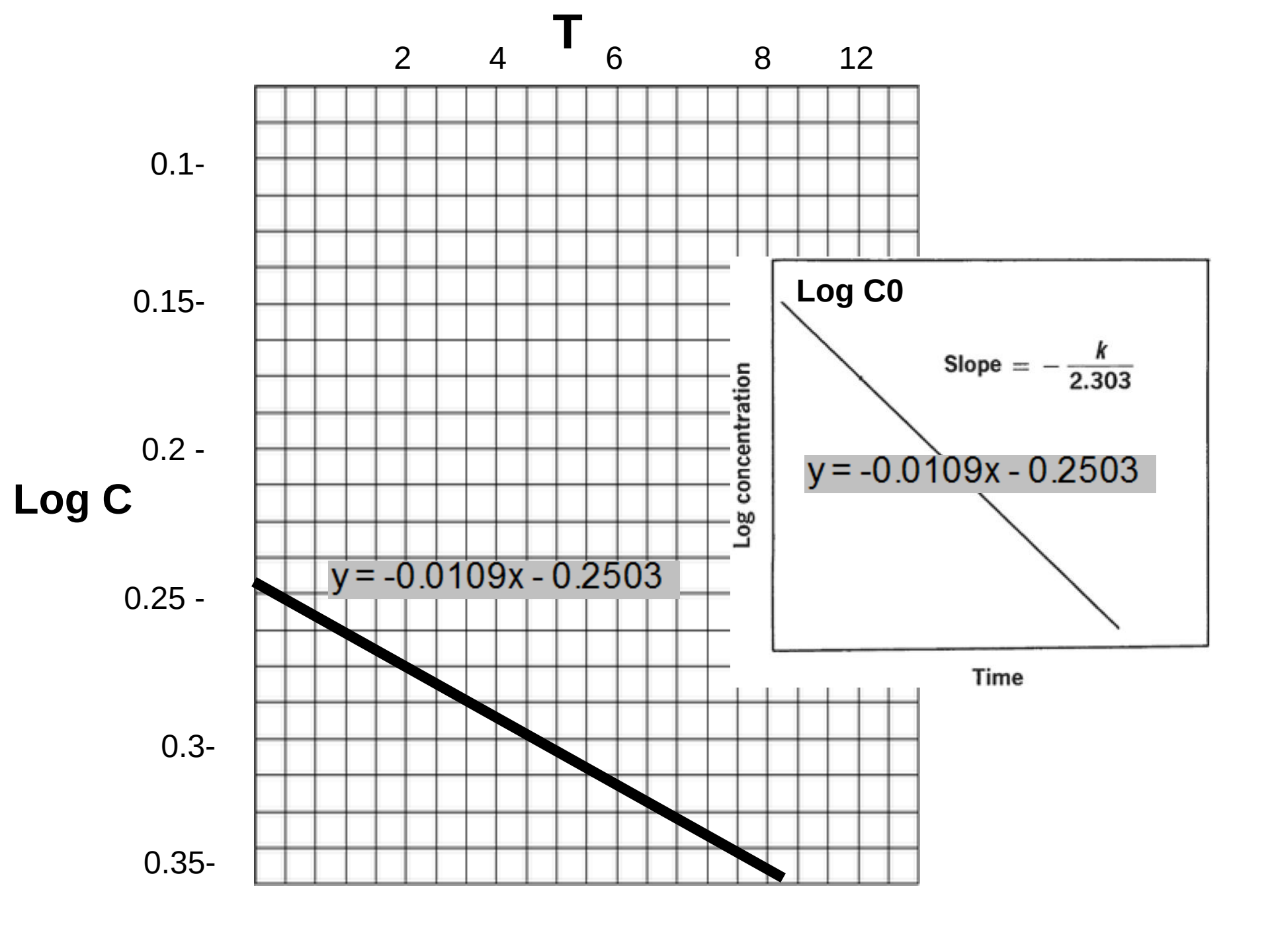
Time (hr)	Glucose, remaining (M)	Log C
0.5	0.552	-0.26
2	0.531	-0.27
3	0.518	-0.28
4	0.502	-0.29
6	0.478	-0.32
8	0.452	-0.34
10	0.431	-0.36
12	0.411	-0.38



y = -0.0109x - 0.2503

slope

intercept


T
2
4
6
8
12
0.1-
0.15-
0.2 -
0.25 -
0.3-
0.35-
Log C
y = -0.0109x - 0.2503
Log C0
Slope = $-\frac{k}{2.303}$
y = -0.0109x - 0.2503
Log concentration
Time

- **the order** ….. First order
- **reaction rate constant** = slope $\frac{y2-y1}{x2-x1}$ = - 001

→ K = - (- 0.01x 2.303) = 0.023 hr-1

- **initial concentration of glucose** = anti log -0.25

= 0.562 M

- **half life** …… $t_{1/2} = 0.693/K = 30.1$ hr

- **What is the remaining concentration after 16 hours.**

Log ct = log 0.562 – 0.023 x 16 / 2.303 = - 0.41

ct = 0.389 M ← **remaining concentration after 16 hours**

- **How long does it take for decomposition of 0.4 M of glucose.**

Log 0.4 = log 0.562 – 0.023 x t /2.303

t= 14.8 hr

Home work

- 1) The half-life of Zn-71 is 2.4 minutes. If one had 100.0 g at the beginning, how many grams would be left after 7.2 minutes has elapsed? Answer 12.5

- 2) 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?**

  Answer 54.25 day

- 3) A solution of a drug contained 100 mg when prepared. How much of the drug will remain after 2 days if the **drug have decomposed to one-half of its original concentration within 10 days ?**Assuming the decomposition is zero order **……Answer 90 mol/L**

- 4) How long will it take for a 40.0 gram sample of I-131 (half-life = 8.040 days) to decay to 1/100 its original mass? **……Answer** 53.5 days

- **1) The half-life of Zn-71 is 2.4 minutes. If one had 100.0 g at the beginning, how many grams would be left after 7.2 minutes has elapsed?**

- **t1/2 = 0.693 /K**
- **K= 0.29 minutes-1**
- **Log Ct = Log C0 – Kt/ 2.303**
- **Log Ct = Log 100 – 0.3x 7.2/ 2.303** =1.06
- Ct= 12.5 **g**

- 2) 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?**

-
- **Log Ct = Log C0 – Kt/ 2.303**
- **Log**300 **= Log** 500 **– K x**40 days **/ 2.303**
- 2.477=2.699- K 17.4
- **K**= 0.013 Sec-1
- **t1/2 = 0.693 /K = 0.693/ 0.011 =** 54.25 day

C0

- 3) A solution of a drug contained 100 mg when prepared. How much of the drug will remain after 2 days if the **drug have decomposed to one-half of its original concentration within 10 days ?**Assuming the decomposition is zero order

$t_{1/2}$

- **$t_{1/2} = C0 / 2 K°$**
- 10 days = 100 mg / 2 **K°**
- **K°** = 100/ 2x10 = 5 mole /L.day
- Ct= **C° - t K°**
- Ct= 100 mg- 2days x 5 = 90 mole /L

- 4) How long will it take for a 40.0 gram sample of I-131 (half-life = 8.040 days) to decay to 1/100 its original mass?

- $t_{1/2} = 0.693/ k$
- K = 0.0862 day -1
- **Log Ct = Log C0 – Kt/ 2.303**
- **Log 0.4 = log 40 – 0.086 t / 2.303**
- **t= 53.5** days

The effect of various factors on drug degradation :

- A number of factors other than concentration may affect the Chemical reaction velocity:

- temperature,
- solvents,
- catalysts,
- light.

Temperature Effects
Collision Theory

- **Reaction rates are expected to be proportional to the number of collisions per unit time.**

- **Because the number of collisions increases as the temperature increases, the reaction rate is expected to increase with increasing temperature.**

- **The application of heat normally increases the rate of chemical reaction . every 10°c increase in temperature normally increase the rate of reaction 2 to 3 times .**

The activation energy

- As a reaction proceeds from reactants to products, the system must pass through a state whose energy is greater than that of the initial reactants.

- This “barrier” is what prevents the reactants from immediately becoming products.

- The activation energy, E_a, is a measure of this barrier.

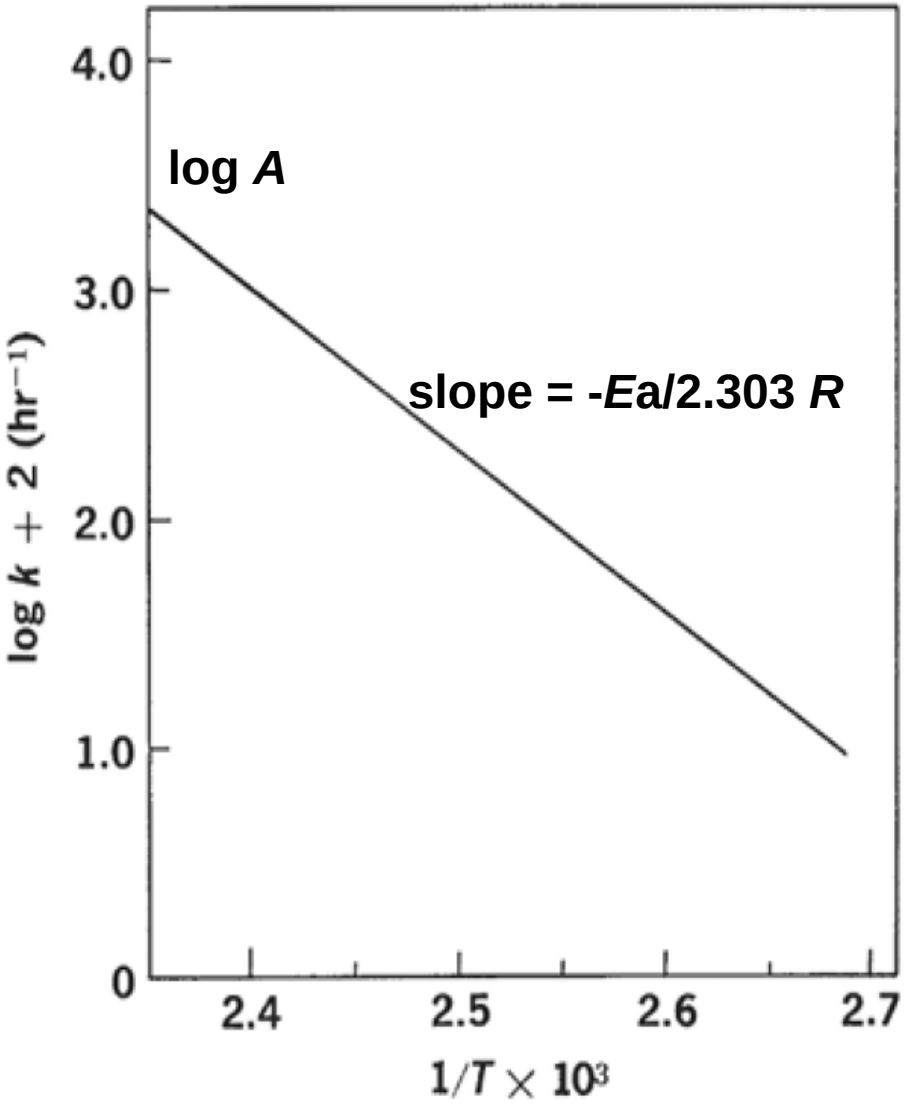
- The effect of temperature on reaction rate is given by the Arrhenius equation:

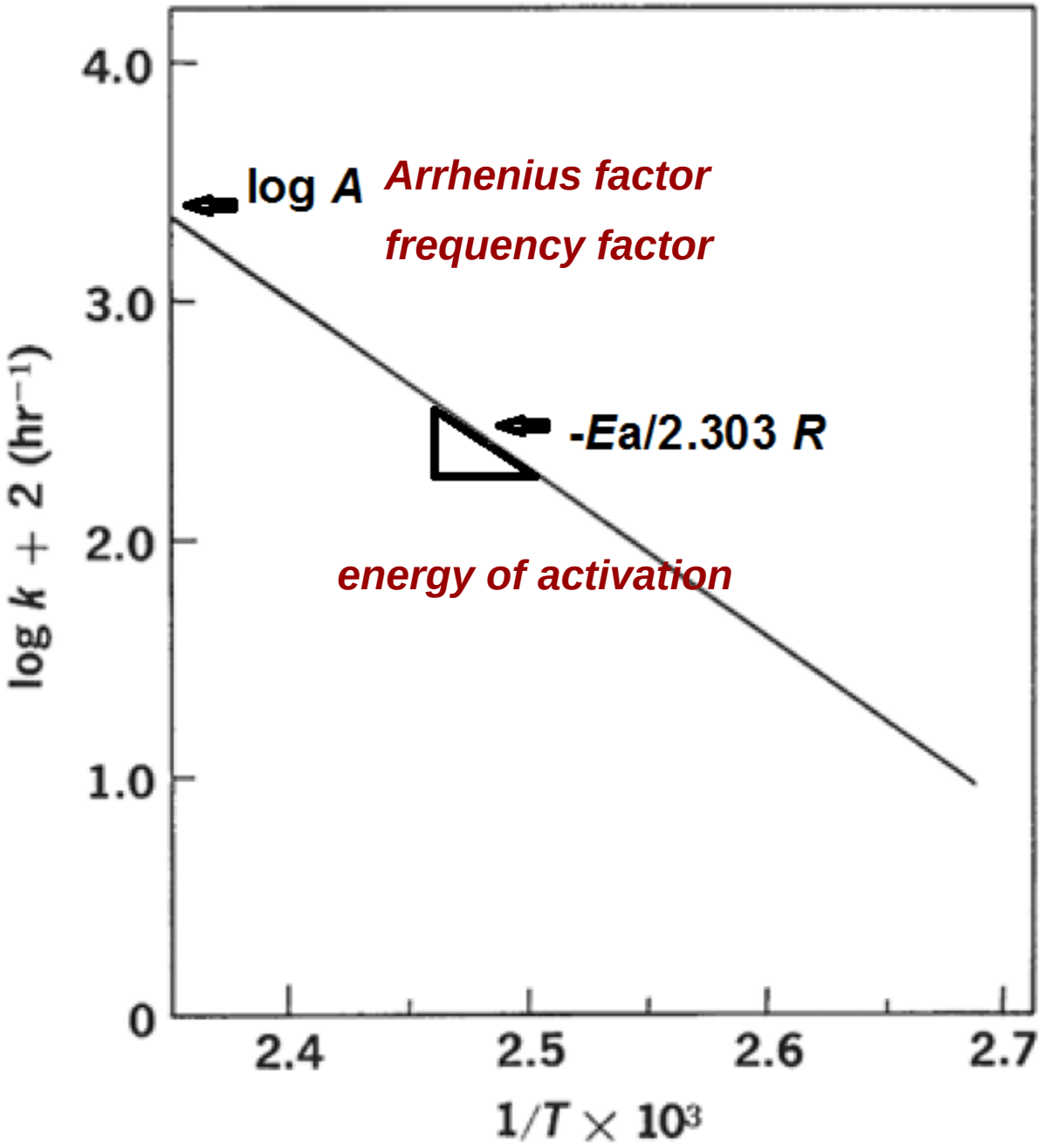
$$k = Ae^{-E_a/RT} \qquad (14\text{–}72)$$

$$\log k = \log A - \frac{E_a}{2.303}\frac{1}{RT} \qquad (14\text{–}73)$$

K **= is the specific reaction rate,**
A **= is a constant known as the *Arrhenius factor* or the *frequency factor*,**
E**a = is the *energy of activation*,**
R **= is the gas constant, 1.987 calories/deg mole,**
T **= is the absolute temperature.**

- **Plotting 1/*T* against log *k*. As seen in equation:**
- **the slope = -*Ea*/2.303**
- **the intercept on the vertical axis is log *A*.**




4.0
3.0
2.0
1.0
0
log k + 2 (hr⁻¹)
log A
Arrhenius factor
frequency factor
-Ea/2.303 R
energy of activation
2.4
2.5
2.6
2.7
1/T × 10³

Accelerated Stability Testing

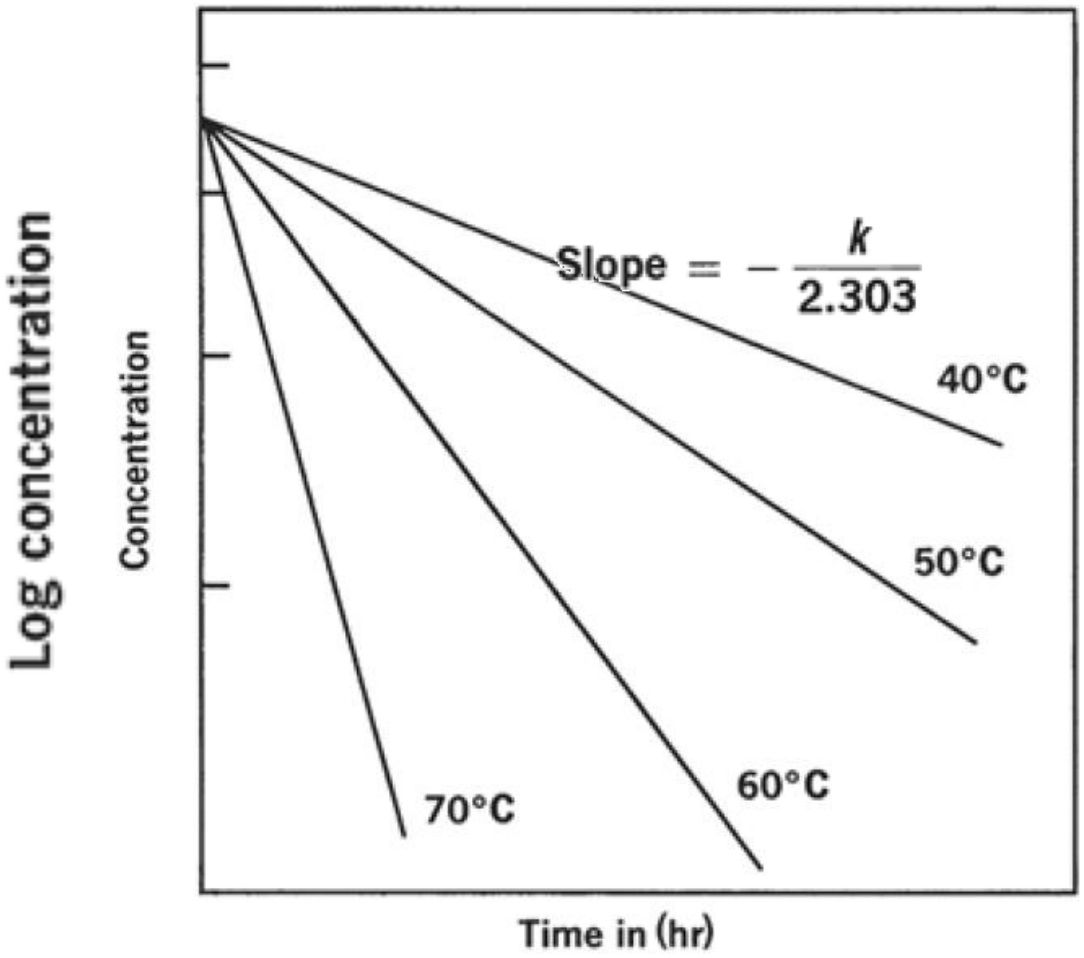
- Accelerated stability studies are **designed to** increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies.

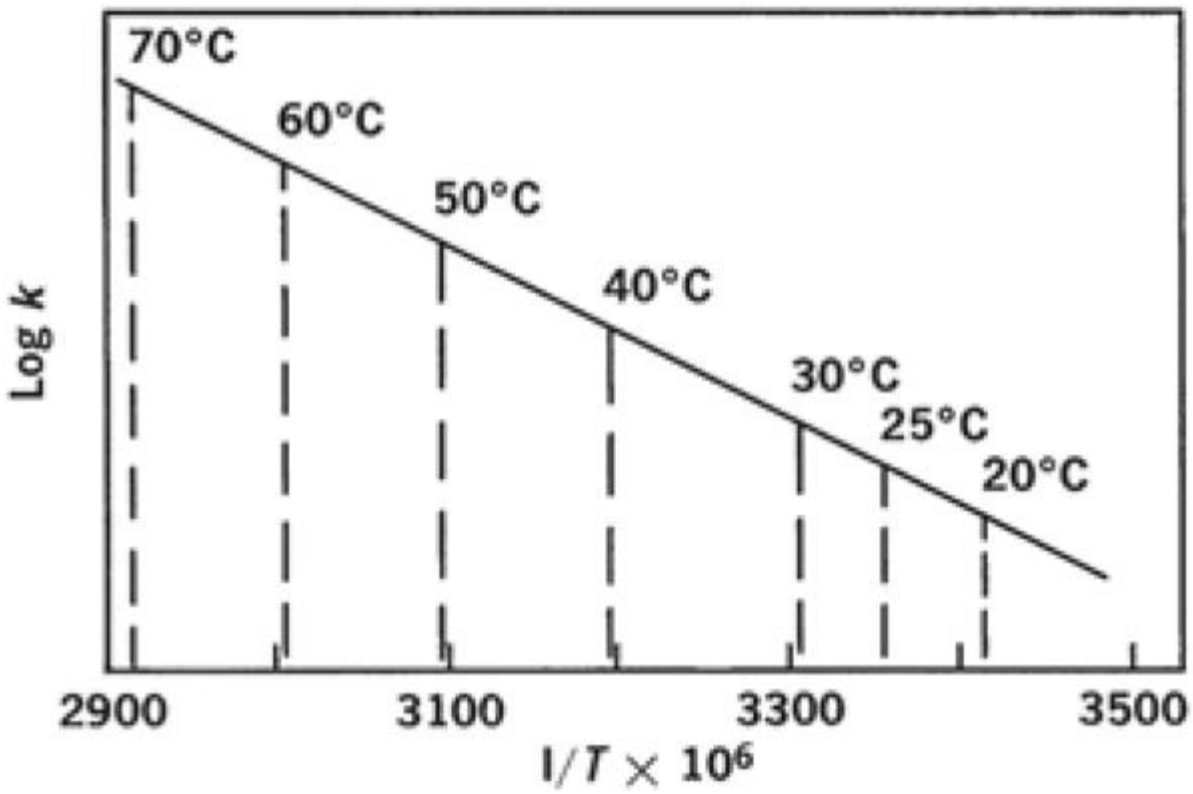
- **Data from these studies**, in addition to long-term stability studies, can be used to assess longer-term chemical effects at non accelerated conditions

- the *k* values for the decomposition of a drug in solution at various elevated temperatures are obtained by plotting some function of concentration against time,

- The logarithms of the specific rates of decomposition are then plotted against the reciprocals of the absolute temperatures

- the resulting line is extrapolated to room temperature. The k_{25} is used to obtain a measure of the stability of the drug under ordinary shelf conditions.


Log concentration
Concentration
Slope = $-\frac{k}{2.303}$
40°C
50°C
60°C
70°C
Time in (hr)


70°C
60°C
50°C
40°C
30°C
25°C
20°C
Log k
2900
3100
3300
3500
1/T × 10^6

Example

- 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 × 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?**

- **Log C_t = Log C_0 – Kt/ 2.303**
- **K = 2.203/t X Log C_0 / C_t**

$$\text{Log } 45 \text{ units/mL} = \text{Log } 94 \text{ units/mL} - \frac{2.09 \times 10\text{-}5 \text{ hr-}1 \; t}{2.203}$$

$$t = 3.5 \times 10^4 \text{ hr} \approx 4 \text{ years}$$

1year x 365 day x 24hr = 8760 hr

Example

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