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Physical pharmacy II

lec4

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Chemical kinetics and stability

Objectives

1-Define reaction rate, reaction order, and molecularity.

2- Understand and apply apparent zero-order kinetics to the practice of pharmacy.

3- Calculate half-life and shelf life of pharmaceutical products and drugs.

4- Describe the influence of temperature, ionic strength, solvent, pH, and dielectric constant on reaction rates.

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 retest period for the drug substance or a **shelf life** for the drug product and recommended storage conditions . Although the pharmaceutical scientist plays a critical role in determining the stability of pharmaceuticals, practicing pharmacists should be able to interpret this information for their patients. It is essential for pharmacists and pharmaceutical scientists to study, understand, and interpret conditions of instability of pharmaceutical products as well as to be able to offer solutions for the stabilization of these products.

- The pharmacist must recognize that alterations in stability may occur **when a drug is combined with other ingredients**. For example, if thiamine hydrochloride(vitamin B_1), which is most stable **at a pH of 2 to 3** and is unstable above **pH 6,** is combined with a buffered vehicle of, say, pH 8 or 9, the vitamin is rapidly inactivated. Knowing the rate at which a drug deteriorates at various hydrogen ion concentrations allows one to choose a vehicle that will retard or prevent the degradation. Patients expect that products will have a reasonable shelf life.
- 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

Fundamentals and concentration effects

Rates, Order, and Molecularity of Reactions

The rate, velocity, or speed of a reaction is given by the expression ***dc/dt*** **,** where *dc* is the increase or decrease of concentration over a minute time interval *dt*. According to the law of mass action, the rate of a chemical reaction is proportional to the product of the molar concentration of the reactants each raised to a power usually equal to the number of molecules, *a* and *b*, of the substances *A* and *B*, respectively, undergoing reaction. In the reaction

$$aA + bB + \cdots = \text{Products}$$

the rate of the reaction is

$$\begin{aligned}\text{Rate} &= \frac{1}{a}\frac{d[A]}{dt} \\ &= \frac{1}{b}\frac{d[B]}{dt} = \cdots k[A]^a[B]^b \cdots\end{aligned}$$

where k is the *rate constant*.

- The overall order of a reaction is the sum of the exponents [a + b, e.g., in equation above of the concentration terms, A and B
- where A is the molar concentration of the reactant. It is an easy matter to replace the units moles/liter by any other units (e.g., pressure in atmospheres) to obtain the proper units for the rate constants if quantities other than concentration are being measured
- The order with respect to one of the reactants, A or B, is the exponent <u>a or b</u> of that particular concentration term. In the reaction of ethyl acetate with sodium hydroxide in aqueous solution, for example

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

the rate expression is

$$\text{Rate} = \frac{d[CH_3COOC_2H_5]}{dt}$$

$$= -\frac{d[NaOH]}{dt} = k[CH_3COOC_2H_5]^1\,[NaOH]^1$$

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). Suppose that in this reaction, sodium hydroxide as well as water was in great excess and ethyl acetate was in a relatively low concentration

Example

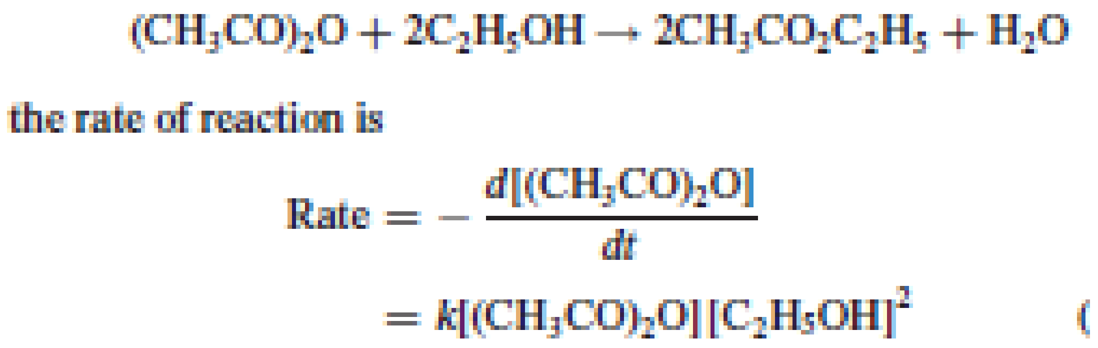
As the reaction proceeded, ethyl acetate would change appreciably from its original concentration, whereas the concentrations of NaOH and water would remain essentially unchanged because they are present in great excess. In this case, the contribution of sodium hydroxide to the rate expression is considered constant and the reaction rate can be written as

$$\frac{d[\mathrm{CH_3COOC_2H_5}]}{dt} = k'[\mathrm{CH_3COOC_2H_5}]$$

where k^1 =k[NaOH]. The reaction is then said to be a **pseudo–first-order reaction** because it depends only on the first power (a=1) of the concentration of ethyl acetate. In general, when one of the reactants is present in such great excess that its concentration may be considered constant or nearly so, the reaction is said to be of pseudo-order

Example

In the reaction of acetic anhydride with ethyl alcohol to form ethyl acetate and water,



$$(CH_3CO)_2O + 2C_2H_5OH \rightarrow 2CH_3CO_2C_2H_5 + H_2O$$

the rate of reaction is

$$\begin{aligned}\text{Rate} &= -\frac{d[(CH_3CO)_2O]}{dt} \\ &= k[(CH_3CO)_2O][C_2H_5OH]^2 \qquad (\end{aligned}$$

What is the order of the reaction with respect to acetic anhydride? With respect to ethyl alcohol? What is the overall order of the reaction? If the alcohol, which serves here as the solvent for acetic anhydride, is in large excess such that a small amount of ethyl alcohol is used up in the reaction, write the rate equation for the process and state the order.

Answer: The reaction appears to be first order with respect to acetic anhydride, second order with respect to ethyl alcohol, and overall third order. However, because alcohol is the solvent, its concentration remains essentially constant, and the rate expression can be written as

$$-\frac{d[(CH_3CO)_2O]}{dt} = k'[(CH_3CO)_2O]$$

Kinetically the reaction is therefore a pseudo–first-order reaction

Determination of Order

The order of a reaction can be determined by several methods.

- ❑ Substitution Method
- ❑ Graphic Method
- ❑ Half-Life Method

Molecularity

molecularity is the **number of molecules, atoms, or ions** reacting in an elementary process. In the reaction

$$Br_2 \rightarrow 2Br$$

the process is unimolecular because the single molecule, Br_2, decomposes to form two bromine atoms. In the single-step reaction

$$H_2 + I_2 \rightarrow 2HI$$

the process is bimolecular because two molecules, one of H_2 and one of I_2, must come together to form the product HI. Termolecular reactions, that is, processes in which three molecules must come together simultaneously, are rare.

Chemical reactions that proceed through more than one step are known as **complex reactions**. The overall order determined kinetically may not be identical with the molecularity because the reaction consists of several steps, each with its own molecularity. For the overall reaction

$$2NO + O_2 \rightarrow 2NO_2$$

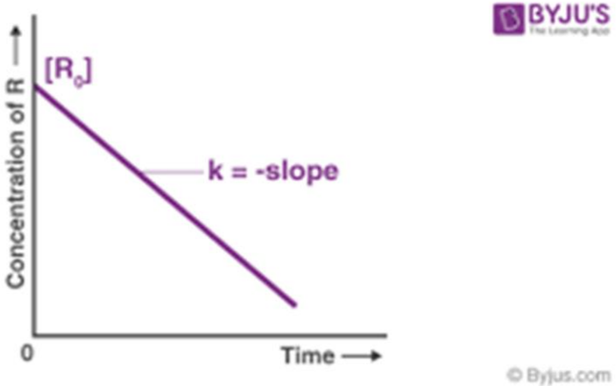
the order has been found experimentally to be **<u>2</u>**. The reaction is not **<u>termolecular</u>**, in which two molecules of (nitric oxide)NO would collide simultaneously with one molecule of O_2. Instead, the mechanism is postulated to consist of two elementary steps, each being bimolecular

$$2NO \rightarrow N_2O_2 \quad \text{slowest step}$$
$$N_2O_2 + O_2 \rightarrow 2NO_2$$

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

➢ Specific Rate Constant

The constant, *k*, appearing in the rate law associated with a single-step (elementary) reaction is called the *specific rate constant* for that reaction. 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. Experimentally, a change of specific rate constant corresponds simply to a change in the slope of the line given by the rate equation. Variations in the specific rate constant are of great physical significance because a change in this constant necessarily represents a change at the molecular level as a result of a variation in the reaction conditions.



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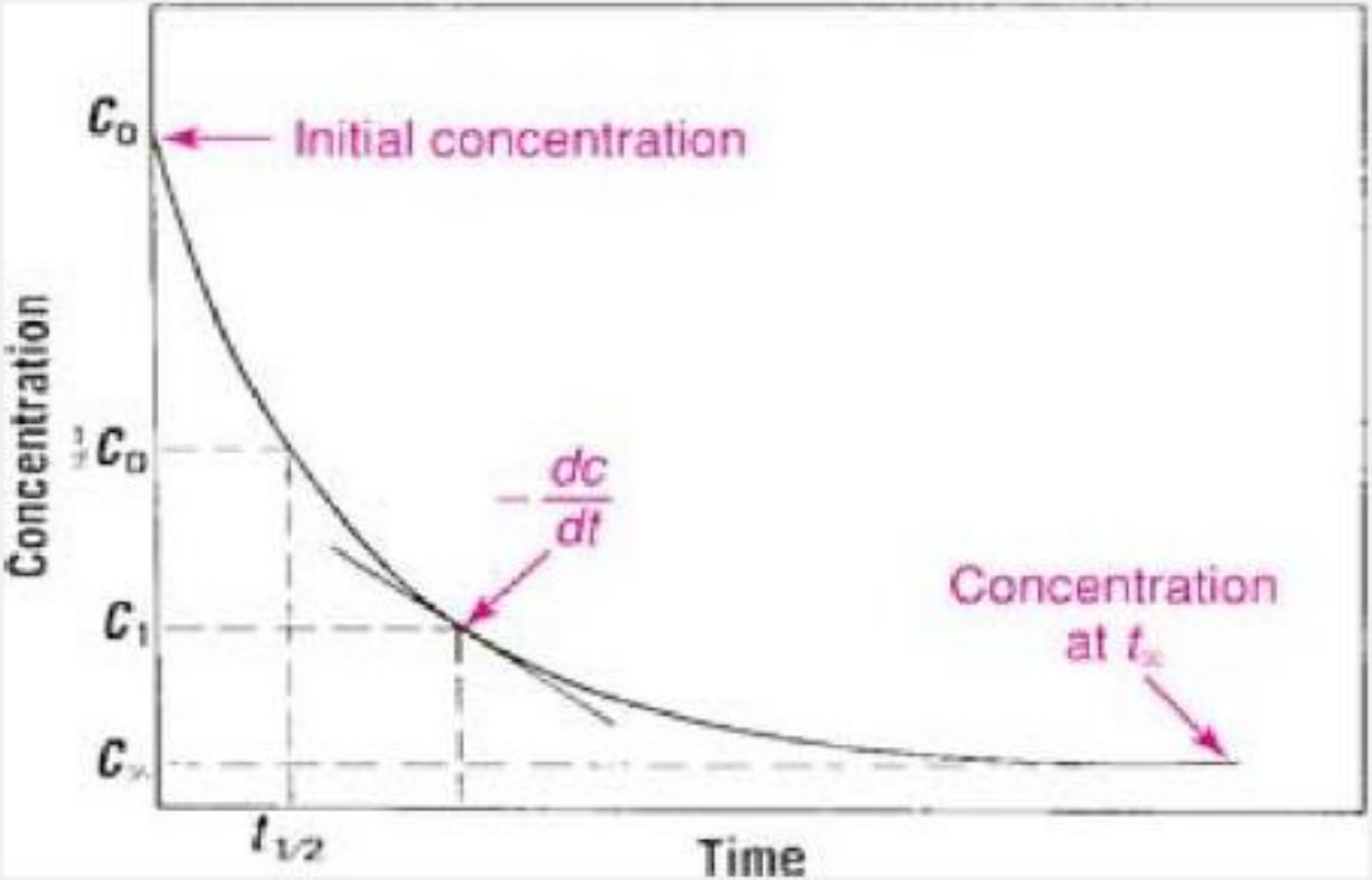
Rate constants derived from reactions consisting of a number of steps of different molecularity are functions of the specific rate constants for the various steps. **Any change** in the nature of a step due to a modification in the reaction conditions or in the properties of the molecules taking part in this step could lead to a **change in the value** of the overall rate constant. At times, variations in an overall rate constant can be used to provide useful information about a reaction, but quite commonly, anything that affects one specific rate constant will affect another; hence, it is quite difficult to attach significance to variations in the overall rate constant for these reactions.

- **Half-life and Shelf life**

The half-life is the time required for one-half of the material to disappear; it is the time at which A has decreased to 1/2 A.

Shelf Life (Expiration Dating)

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).


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

Apparent or pseudo-order

“Apparent” or “pseudo”-order describes a situation where one of the reactants is present in large excess or does not effect the overall reaction and can be held constant. For example, many hydrolysis decomposition reactions of drug molecules are second order. Usually the amount of water present is in excess of what is needed for the reaction to proceed. In other words, the concentration of water is essentially constant throughout the reaction. In this case, the second-order reaction behaves like a first-order reaction and is called an apparent or pseudo–first order reaction

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

$$A_t = A_0 - k_0 t$$

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

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

A_t or c_t = remaining concentration of reactants

- k= constant reaction rate
- t= time
- A_0 or C_0= initial concentration of reactants
- $t_{1/2}$ = half life

at units

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

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

Clarification

dc/dt =K

$A_t=A_0 - K_0t$

zero=A_0-K_0t

$A_0=K_0t$................$\frac{A0}{2} = \frac{K0t}{2}$

$\frac{1}{2}A_0=K_0t^{1}/_{2}$

zero-order reaction

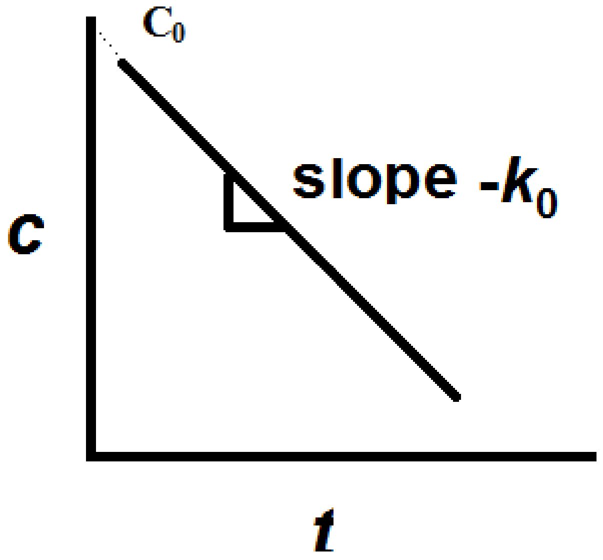
$$t_{1/2} = \frac{\frac{1}{2}A_0}{k_0}$$

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

$$A_t = A_0 - k_0 t$$



Because the half-life is the time required for one-half of the material to disappear, then:

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

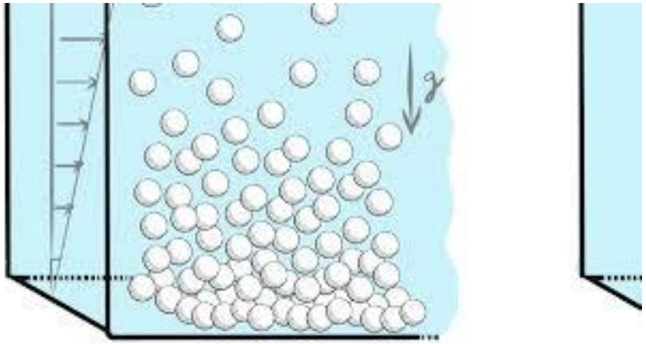
$$t_{1/2} = \frac{\frac{1}{2} A_0}{k_0}$$

The shelf life is (0.1A°./ K°).

Suspensions. Apparent Zero-Order Kinetics

Suspensions are another case of zero-order kinetics, in which the concentration in solution depends on the **<u>drug’s solubility</u>**. As the drug decomposes in solution, more drug is released from the suspended particles so that the concentration remains constant. This concentration is, of course, the drug’s equilibrium solubility in a particular solvent at a particular temperature. The important point is that the amount of drug in solution remains constant despite its decomposition with time. The reservoir of solid drug in suspension is responsible for this constancy.

It is referred to as an apparent zero-order equation, being zero order only because of the **suspended drug reservoir**, which ensures constant concentration. Once all the suspended particles have been converted into drug in solution, the system changes to a first-order reaction



Example

Shelf Life of an Aspirin Suspension(zero order)

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.

Answer:

$$k_0 = k \times [\text{Aspirin in solution}]$$

The shelf life is $(t_{90}) = \dfrac{0.1A°}{K°}$

(day=86400sec.)

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

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

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

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

First-Order Reactions

When the rate of the reaction is proportional to the first power of concentration of the reactant

Log C_t = Log C_0 – K_t/ 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

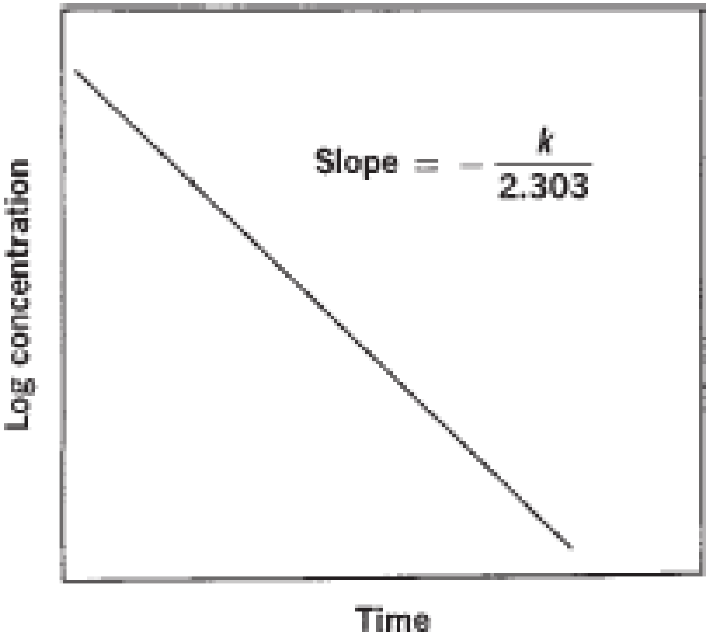
- C_0 = initial concentration
- K= reaction rate constant
- $t_{1/2}$ = half life

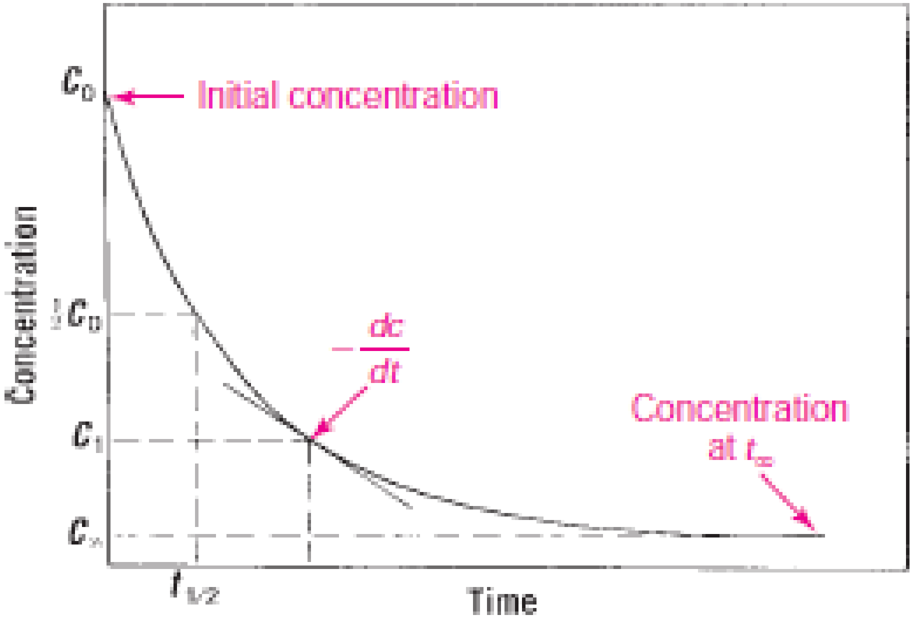
<u>at units</u>

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

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

$$\mathrm{Log}\ C_t = \mathrm{Log}\ C_0 - K_t / 2.303$$





Example 1

Decomposition of Hydrogen Peroxide(**First-Order Reactions)**

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

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

(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 2

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

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

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

In Example 2, the drug has decomposed by 250 units/mL in the first 54.3 days. Because the half-life is a constant, independent of the concentration, it remains at 54.3 days regardless of the amount of drug yet to be decomposed. In the second half-life of 54.3 days, half of the remaining 250 units/mL, or an additional 125 units/mL, are lost; in the third half-life, 62.5 units/mL are decomposed, and so on.

Half-Life

The period of time required for a drug to decompose to one half of the original concentration as calculated in Example 1 is the half-life, $t_{1/2}$, for a first-order reaction

$$t_{1/2} = \frac{2.303}{k} \log \frac{500}{250} = \frac{2.303}{k} \log 2$$

$$t_{1/2} = \frac{0.693}{k}$$

Second-Order Reactions

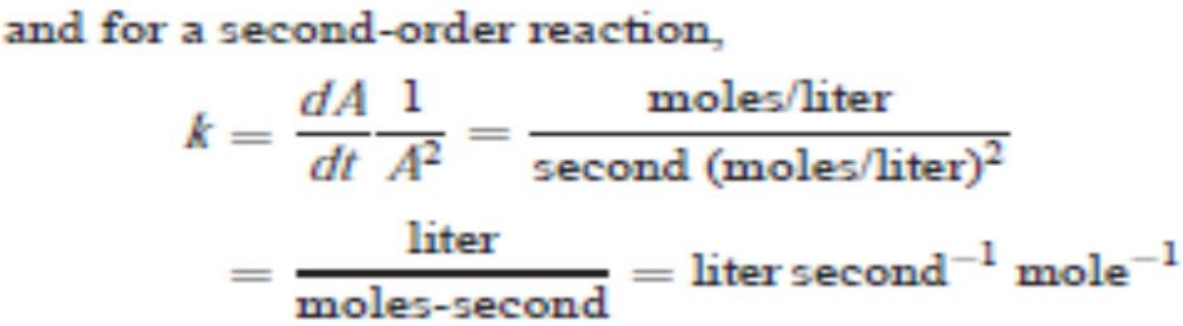
The rates of bimolecular reactions, which occur when two molecules come together,

A + B → Products

are frequently described by the second-order equation. When the **speed of the reaction depends on the concentrations of A and B** with each term raised to the first power, the rate of decomposition of A is equal to the rate of decomposition of B, and both are proportional to the product of the concentrations of the reactants:

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

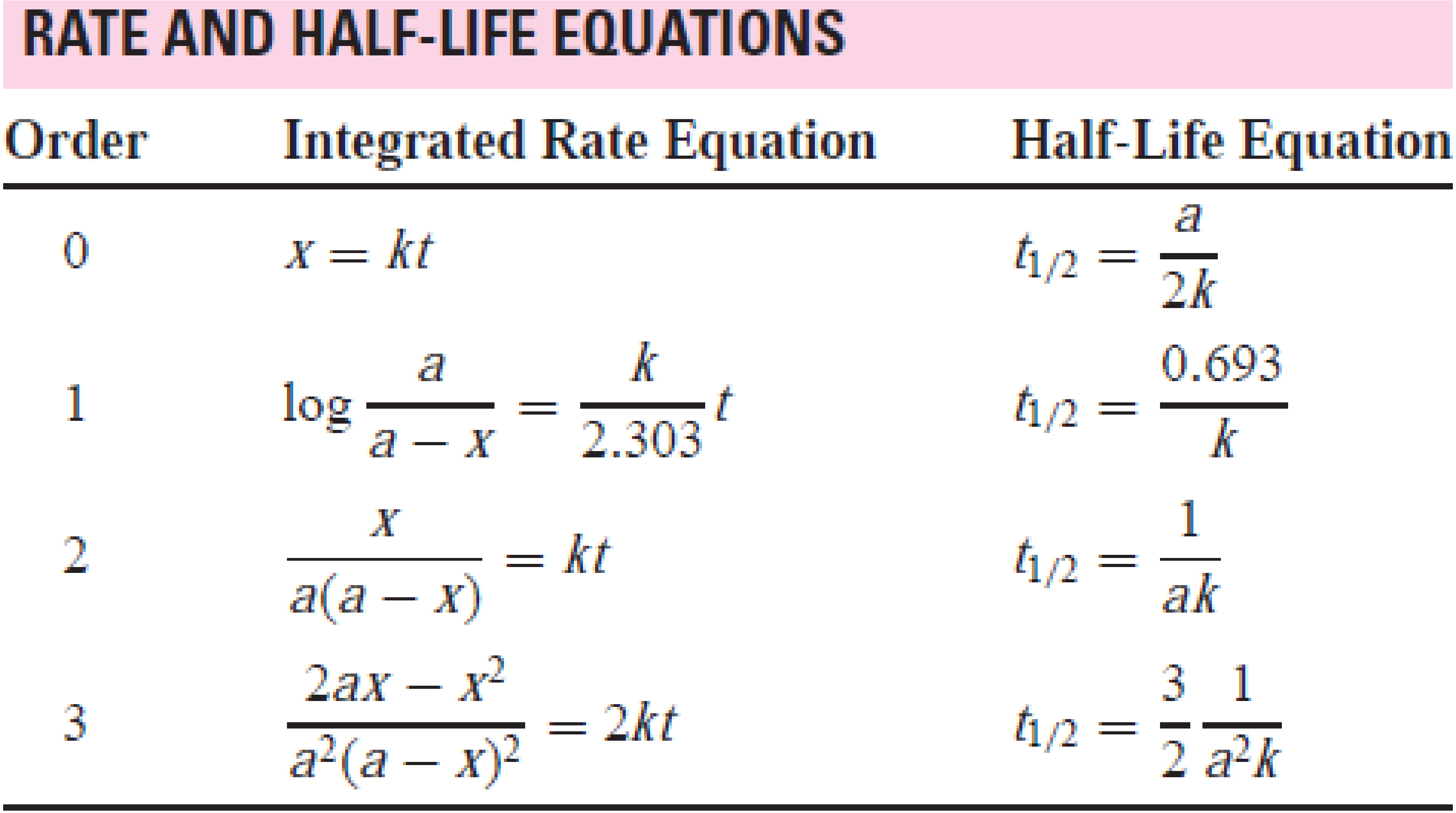
at units



and for a second-order reaction,

$$k = \frac{dA}{dt}\frac{1}{A^2} = \frac{\text{moles/liter}}{\text{second (moles/liter)}^2}$$

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



RATE AND HALF-LIFE EQUATIONS

Order	Integrated Rate Equation	Half-Life Equation
0	$x = kt$	$t_{1/2} = \dfrac{a}{2k}$
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	$\dfrac{2ax - x^2}{a^2(a-x)^2} = 2kt$	$t_{1/2} = \dfrac{3}{2}\dfrac{1}{a^2k}$

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.

speed of many reactions increases about two to three times with each 10° rise in temperature. 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 equation, first suggested by Arrhenius

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

➢ Medium Effects: Solvent, Ionic Strength, Dielectric Constant

Effect of the Solvent

The influence of the solvent on the rate of decomposition of drugs is a topic of great importance to the pharmacist. Although the effects are complicated and generalizations cannot usually be made, it appears that the reaction of nonelectrolytes is related to the relative internal pressures or solubility parameters of the solvent and the solute.

The effects of the ionic strength and the dielectric constant of the medium on the rate of ionic reactions are also significant.

➢ Catalysis: Specific and General Acid–Base and pH Effects

As already noted, the rate of a reaction is frequently influenced by the presence of a catalyst. Although the hydrolysis of sucrose in the presence of water at room temperature proceeds with a decrease in free energy, the reaction is so slow as to be negligible. When the hydrogen ion concentration is increased by adding a small amount of acid, however, inversion proceeds at a measurable rate.

➢ Specific Acid–Base Catalysis

Solutions of a number of drugs undergo accelerated decomposition on the addition of acids or bases. If the drug solution is buffered, the decomposition may not be accompanied by an appreciable change in the concentration of acid or base so that the reaction can be considered to be catalyzed by hydrogen or hydroxyl ions

Stability of pharmaceuticals

Decomposition and Stabilization of Medicinal Agents

Pharmaceutical decomposition can be classified as **hydrolysis**, **oxidation**, **isomerization**, **epimerization**, and **photolysis**, and these processes may affect the stability of drugs in liquid, solid, and semisolid products. The study of photochemical reactions requires strict attention to control of the wavelength and intensity of light and the number of photons actually absorbed by the material. Reactions that occur by photochemical activation are usually complex and proceed by a series of steps. The rates and mechanisms of the stages can be elucidated through a detailed investigation of all factors involved, but in this elementary discussion of the effect of light on pharmaceuticals, we will not go into such considerations.

Photodegradation

Light energy, like heat, may provide the activation necessary for a reaction to occur. **Radiation** of the proper frequency and of sufficient energy must be absorbed to activate the molecules. The energy unit of radiation is known as the **photon** and is equivalent to one quantum of energy. Photochemical reactions do not depend on temperature for activation of the molecules; therefore, the rate of activation in such reactions is independent of temperature. After a molecule has absorbed a quantum of radiant energy, however, it may collide with other molecules, raising their kinetic energy, and the temperature of the system will therefore increase. The initial photochemical reaction may often be followed by thermal reactions.

note

quantum (plural quanta) is the minimum amount of any physical entity

Containers and Closures

A container closure or packaging system refers to the sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product. Packaging components are typically made from glass, high-density polyethylene resin, metal, or other materials. Typical components are containers (e.g., ampules, vials, bottles), container liners (e.g., tube liners), closures (e.g., screw caps, stoppers), closure liners, stopper overseals, container inner seals, administration ports (e.g., on large-volume parenterals), overwraps, administration accessories, and container labels. A package or market package refers to the container closure system and labeling, associated components (e.g., dosing cups, droppers, spoons), and external packaging (e.g., cartons or shrink wrap).

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?

We have

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

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


THANK YOU!

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