CHEMICAL KINETICS AND STABILITY

● The stability of drug product with time is important in determination of shelf life and expired date.

● The stability affected by factors, such as temperature, humidity, and light. This chapter studies the rates and mechanisms of reactions specially the decomposition and stabilization of drug products.

● For example, thiamine hydrochloride is most stable at a pH of 2 to 3 and is unstable above pH 6, so in preparation, the pharmacist should select the buffered vehicle that prevents the degradation.

● Applications of chemical kinetics in pharmacy result in the production of more-stable drug preparations.

FUNDAMENTALS AND CONCENTRATION EFFECTS

Rates, Order, and Molecularity of Reactions

Molecularity

● Molecularity is the number of molecules, atoms, or ions reacting in an elementary process. molecularity classify the reaction into unimolecular, bimolecular, and Termolecular. ● molecularity cannot gives complete detail about order of reaction specially those of several steps while kinetic study gives details.

● Example: $Br_2 \longrightarrow 2Br$ unimolecular

$H_2 + I_2 \longrightarrow 2HI$ bimolecular

$2NO + O_2 \longrightarrow 2NO_2$ Termolecular
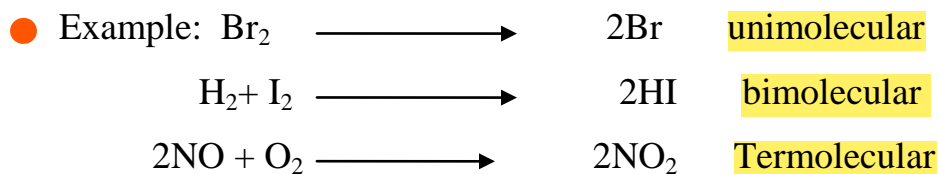
While the real detail mechanism revealed by kinetic study as follows:

$2NO \rightleftarrows N_2O_2$ (Fast)

$N_2O_2 + O_2 \longrightarrow 2NO_2$ (Slow)
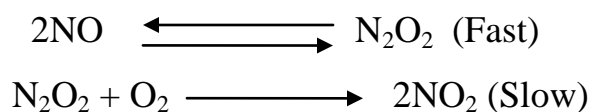
The rate of the reaction is given by the slow step.

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Rate

● 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 an infinitesimal time interval dt.

● In the reaction

Reactant ⟶ Products
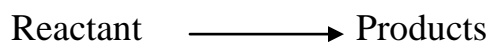
$$\text{Rate} = - \frac{d[Reactant]}{dt} = K[Reactant]^a$$

where k is the rate constant and exponent a represent the order of reaction.

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.

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

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

Kinetic study

Zero-Order Reactions

● Garrett found that the loss in color of a multisulfa product followed a zero-order rate. The rate expression for the change of concentration, C, with time is therefore

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

● It means that the rate of reaction not depend on concentration of reactant, it is constant with time.
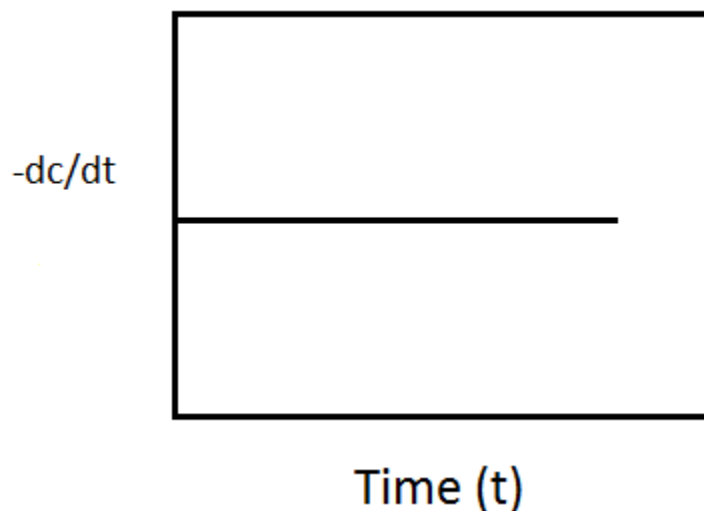
Time (t)

The rate equation can be integrated between the initial concentration, C_0, at t = 0, and C_t, the absorbance after time (t):
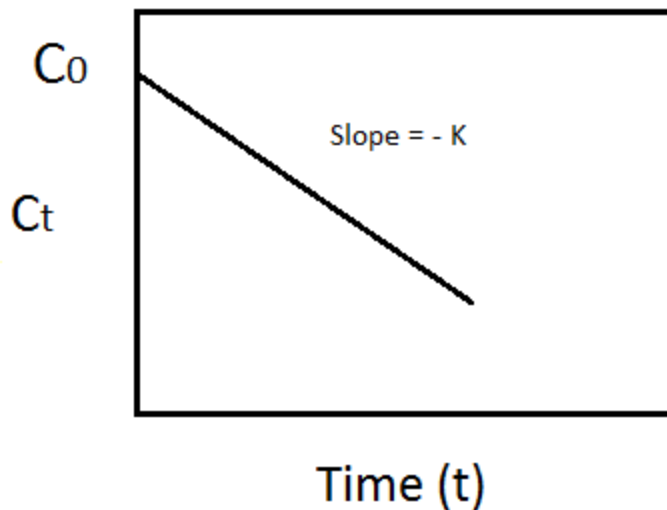
$$C_t = C_o - k_o t$$

$$t = \frac{Co - Ct}{ko}$$

Note:
The straight-line equation is:
y=mx+c
m is the gradient and
c is the height at which the line crosses the y-axis, also known as the y-intercept.

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Time (t)

● Because the half-life is the time required for one-half of the material to disappear, in the present case, after one half, the concentration becomes $1/2C_o$.

$$t_{1/2} = \frac{Co - 1/2Co}{ko}$$

$$t_{1/2} = \frac{\frac{1}{2}Co}{ko}$$

● For shelf life

$$t_{90\%} = \frac{Co - 0.9Co}{ko} = \frac{0.1C0}{K0}$$

- The unit of zero order rate constant is:

$$k_0 = -\frac{dC}{dt} = \frac{mole/liter}{second} = \frac{mole}{liter\ second} = \text{mole liter}^{-1}\text{second}^{-1}$$

First-Order Reactions

● Harried showed that the decomposition rate of hydrogen peroxide catalyzed by 0.02 M KI was proportional to the concentration of hydrogen peroxide remaining in the reaction mixture at any time. The data for the reaction
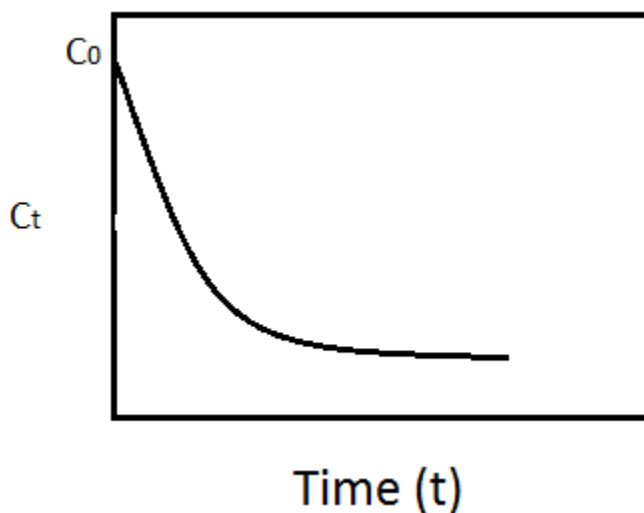
$$2H_2O_2 = 2H_2O + O_2$$

Although two molecules of hydrogen peroxide appear in the equation, the reaction was found to be first order.

The rate equation is written
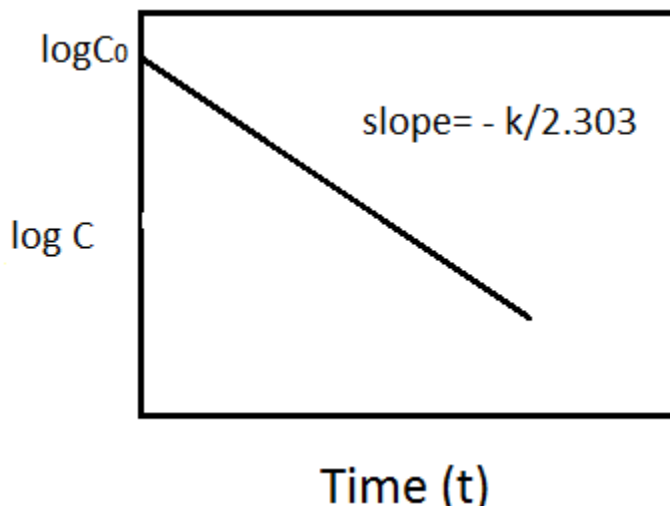
$$-\frac{dC}{dt} = k\,C$$

where c is the concentration of hydrogen peroxide remaining undecomposed at time t and k is the first-order rate constant.

Integrating above equation, we have

$$\ln C = \ln C_0 - Kt$$

(Common logarithm) $$\log C = \log C_0 - \frac{k}{2.303}\, t$$

For calculation of half life of reaction follows first order;

$$\log \frac{C0}{Ct} = \frac{K\,t}{2.303}$$

at half life; t= t1/2, Ct= ½ C$_0$

$$\log \frac{C0}{\tfrac{1}{2}\,C0} = \frac{K\,t1/2}{2.303}$$

$$t\,½ = 0.693/k$$

For shelf life t$_{90}$;

$$\log \frac{C0}{0.9\,C0} = \frac{K\,t10\%}{2.303} \quad , \qquad t_{90} = 0.105/k$$

- The unit of first order rate constant is:

$$k = -\frac{dC}{dt}\frac{1}{C} = \frac{mole/liter}{second.mole/liter} = \frac{1}{second} = second^{-1}$$

Determination of Order

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

1. **Substitution Method**. The data from kinetic study can be substituted in the equations for each order. When the calculated k values remain constant for different Ct, the reaction is considered to be of that order.

2. **Graphic Method**. A plot of the data in the form of a graph can also be used to ascertain the order.
If a straight line results when concentration is plotted against t, the reaction is zero order.
The reaction is first order if log (concentration) versus t yields a straight line, and it is second-order if 1/(concentration) versus t gives a straight line.

3. **Half-Life Method**. In a zero-order reaction, the half-life is proportional to the initial concentration, a, as observed in Table 15-2. The half-life of a first-order reaction is independent of initial concentration a;
t1/2 for a second-order reaction, in which a = b, is proportional to 1 /a.

Suspensions, Apparent Zero-Order Kinetics

- Suspensions are another case of zero-order kinetics, in which the concentration in solution depends on the drug's solubility. As the drug decomposes in solution, more drug is released from the suspended particles, so that the concentration remains constant. The equation for an ordinary solution, with no reservoir of drug to replace that depleted, is the first-order expression, equation

$$-d[C]/dt = k_f[C]$$ where c= concentration of drug in solution

= solubility

K_f= first order rate constant of solution

When the concentration [C] is rendered constant, as in the case of a suspension, we can write

$$K_f [C] = K_0$$ where K_0= zero order rate constant of suspension

Thus, $K_0 = K_f$ x Solubility

$$-d[C]/dt = K_0$$

Second-Order Reactions

- The rates of bimolecular reactions, which occur when two molecules come together, are frequently described by the second-order equation.

$$A + B \longrightarrow Products$$

- 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:

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

● If a and b are the initial concentrations of A and B respectively, and x is the concentration of each species reacting in time t, the rate law can be integrated and written according to 3 possibilities:

1. When, in the simplest case, both A and B are present in the same concentration so that a = b,

$$\frac{x}{a(a-x)} = Kt$$

The rate constant, k, in a second-order reaction therefore has the dimensions liter/ (mole sec) or liter mole^{-1} sec^{-1}.

The half-life of a second-order reaction is

$$t1/2= 1/ak$$

2. When, in the general case, A and B are not present in equal concentrations but the difference in concentration is not big, integration of equation yields:

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

3. When A and B are not present in equal concentrations and the difference in concentration is very big

(*Pseudo-first-order reaction*):

Suppose that in this reaction, A was in great excess and B was in a relatively low concentration.

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

$$A + B \longrightarrow \text{Products}$$

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

K is constant and [A] is constant

$$- \frac{d[B]}{dt} = K'\,[B]$$

where K'= K [A], K'= Pseudo-first-order constant