Physical Pharmacy

Chemical Kinetics and Stability
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.
The overall order of a reaction is the sum of the exponents of the concentration terms.

The order with respect to one of the reactants, A or B, is the exponent \(a\) or \(b\) of that particular concentration term.

\[
CH_3COOC_2H_5 + NaOH \rightarrow CH_3COONa + C_2H_5OH
\]

\[
Rate = \frac{d[CH3COOC2H5]}{dt} = \frac{d[NaOH]}{dt} = k[CH3COOC2H5]^1[NaOH]^1
\]

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.

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

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

where \( k' = k[\text{NaOH}] \). 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.
Zero-Order Reactions

\[ -\frac{dA}{dt} = K_0 \]

\[ A = A_0 - K_0 t \]

\[ t_{1/2} = \frac{0.5 A_0}{K_0} \]

■ 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 \(-k_0\).
\[ [A]_0 \]

\[ [A]_t \]

slope = -k
First-Order Reactions

\[ \frac{dc}{dt} = kc \]

- where \( c \) is the concentration remaining undecomposed at time \( t \) and \( k \) is the first-order velocity constant

\[ \log c = \log c_0 - k \frac{t}{2.303} \quad c = c_0 10^{-\frac{kt}{2.303}} \]

\[ k = \frac{2.303}{t} \log \frac{a}{a - x} \]

- where the symbol \( a \) is customarily used to replace \( c_0 \), \( x \) is the decrease of concentration in time \( t \), and \( a - x = c \).
First-Order Reactions

- The concentration decreases exponentially with time.
- The concentration begins at $c_0$ and decreases as the reaction becomes progressively slower.
- The concentration asymptotically approaches a final value $c_\infty$ as time proceeds toward infinity.
Half-Life for First-order

The period of time required for a drug to decompose to one-half of the original concentration.

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

\[
t_{1/2} = \frac{0.693}{k}
\]
Second-Order Reactions

\[ k = \frac{2.303}{t(a-b)} \log \frac{b(a-x)}{a(b-x)} \]
Second-order
Integrated rate equation

\[ \frac{1}{[A]_t} = \frac{1}{[A]_0} + 2kt \]

2A \rightarrow B

time, \( t \)

slope = + 2k

intercept = \( \frac{1}{[A]_0} \)
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. 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.
Suspensions. Apparent Zero-Order Kinetics

- The equation for an ordinary solution, with no reservoir of drug to replace that depleted, is the first-order expression:

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

- where \([A]\) is the concentration of drug remaining undecomposed at time \(t\), and \(k\) is known as a first-order rate constant. When the concentration \([A]\) is rendered constant, as in the case of a suspension, we can write

\[k[A] = K_0\]

\[- \frac{d[A]}{dt} = K_0\]

- 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.
Shelf Life of an Aspirin Suspension

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. 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.
Shelf Life of an Aspirin Suspension

\[ k_0 = k \times [\text{Aspirin in solution}] \]
\[ k_0 = (4.5 \times 10^{-6} \text{ sec}^{-1}) \times (0.33 \text{g}/100\text{ml}) \]
\[ k_0 = 1.5 \times 10^{-6} \text{ g}/100\text{ml sec}^{-1} \]

\[ t_{90} = \frac{0.10[A]_0}{K_0} = \frac{(0.10 \times 6.5)}{1.5 \times 10^{-6}} = 4.3 \times 10^5 = 5\text{days} \]
Determination of Order

- **Substitution Method**

  - The data accumulated in a kinetic study can be substituted in the integrated form of the equations that describe the various orders.

  - When the equation is found in which the calculated \( k \) values remain constant within the limits of experimental variation, the reaction is considered to be of that order.
Determination of Order

- **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 $\log \left( a - x \right)$ versus $t$ yields a straight line,

- and it is second order if $1/(a - x)$ versus $t$ gives a straight line (in the case in which the initial concentrations are equal).
Determination of Order

- **Half-Life Method**

- In a zero-order reaction, the half-life is proportional to the initial concentration, \( a \).

- The half-life of a first-order reaction is independent of \( a \);

- \( t_{1/2} \) for a second-order reaction, in which \( a = b \), is proportional to \( 1/a \);
**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.

  - In fact, the 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,
Temperature Effects

where $k$ 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, and $T$ is the absolute temperature.

\[ k = Ae^{-E_a/RT} \]

\[ \log k = \log A - \frac{E_a}{2.303RT} \]
Temperature Effects

Fig. 14-6. A plot of log $k$ against $1/T$ for the thermal decomposition of glucose.
Accelerated Stability Testing

- It is not practical to wait for years to observe how long it takes for a drug to decompose.
- Various types of stress are applied to drug compounds to speed the process.
- Temperature increase can accelerate the reaction, therefore drugs are stored a variety of higher temperatures.
- High humidity increases the decomposition process by hydrolysis.
- Artificial lights are used to increase the effect of daylight on a drug product.
Accelerated Stability Testing

- At various time periods, samples are taken and analyzed for the viability of the active contents.

- Practically by using elevated temperatures, the k values for a drug can be found under decomposition in solution by plotting a function of the concentration versus time.
Fig. 14-19. Accelerated breakdown of a drug in aqueous solution at elevated temperature.
Fig. 14-20. Arrhenius plot for predicting drug stability at room temperatures.
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 $2.09 \times 10^{-5}$ 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?
Example

\[ t = \frac{2.303}{k} \log \frac{c_0}{c} \]

\[ = \frac{3.5 \times 10^4 \text{ hr}}{2.303} \log \frac{45}{94} = 3.5 \times 10^4 \text{ hr} \approx 4 \text{ years} \]
Fig. 14-21: Time in days required for drug potency to fall to 90% of original value. These times, designated $t_{90}$, are then plotted on a log scale in Figure 14-22.