KINETICS AND DRUG STABILITY
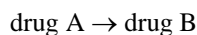
Syllabus:

General considerations and concepts, half life determination. Influence of temperature, light, solvent, catalytic species and other factors. Accelerated stability study, calculation of expiry date.

Rate

The rate of a chemical reaction of process is the velocity with which the reaction occurs.

Let us consider the following reaction:

drug A → drug B

If the amount of the drug A is decreasing with respect to time (i.e. the reaction is going in a forward direction), then the rate of this reaction can be expressed as follows:

$-\dfrac{dA}{dt}$ The negative sign appears because concentration of drug A decreases with time.

Since the amount of drug B is increasing with respect to time, the rate of the reaction can also be expressed as:

$+\dfrac{dB}{dt}$ The positive sign appears because the concentration of the product B increases with time.

Usually, in pharmacokinetics, only the parent (or pharmacologically active) drug is measured experimentally. The metabolites of the drug or the products of the decomposition of the drug may not be known or may be very difficult to quantitate. Hence, The rate of a reaction is determined experimentally by measuring the disappearance of drug A at given time intervals.

Order of a reaction

If C is the concentration of drug A, the rate of decrease in C (of drug A) can be expressed by a general

expression as function of time, t as: $\dfrac{dC}{dt} = -kC^n$ ....eqn. 1

Where k = rate constant and n = **order of the reaction**.

If n = 0 then the reaction is called a zero-order reaction,

if n = 1 then the reaction is called a first-order reaction.

if n = 2 then the reaction is called a second order reaction.

If a reaction is: aA + bB → Product

and if the reaction rate $= -k\,[A]^a\,[B]^b$ then the reaction is said to be (a + b) order.

Example: In the reaction of ethyl acetate and sodium hydroxide in aqueous solution, for example,

$CH_3COOC_2H_5 + NaOH_{soln}$ → $CH_3COONa + C_2H_5OH$
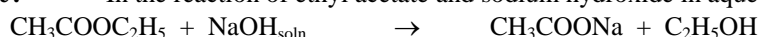
the rate expression is

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

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 and water was in great excess and ethyl acetate was in a relatively low concentration. In this case the concentration of sodium hydroxide may be taken as constant and the rate equation can then be written as:

$$Rate = -\frac{d[CH_3COOC_2H_5]}{dt} = k'[CH_3COOC_2H_5]^1$$

in which k' = k [NaOH]. The reaction is then said to be *pseudo-first order*, because it only depends on the first power (a = 1) of the concentration of ethyl acetate.

* The overall order of a reaction is determined by experiments.

Molecularity of a reaction

The over all reaction may take place by several steps. Each step is called an elementary step. The order of each elementary step is the number of reactant molecules taking part in that reaction, hence, the order of an elementary step is called the molecularity of the reaction.

	Reaction	Order	Molecularity
Elementary reaction -I	$2\,NO \rightarrow N_2O_2$.	Second Rate = k $[NO]^2$.	Bimolecular
Elementary reaction – II	$N_2O_2 + O_2 \rightarrow 2NO_2$.	Second Rate = k $[N_2O_2][O_2]$	Bimolecular
Overall reaction	$2NO + O_2 \rightarrow 2NO_2$.	Second Found from experiment	

Specific rate constant

The constant k associated with a single step (elementary) reaction is called a specific rate constant for that reaction. If the specific rate constant of an elementary reaction is changed by some factors (like temperature, light, catalyst, solvents etc.) then the overall reaction rate will also change.

Zero-Order Reactions

If the concentration of drug A is decreasing at a constant time interval t. then the rate of disappearance of drug A is expressed as:

$$\frac{dC}{dt} = -k_0 \qquad \text{..............................eqn. 2}$$

The term k_0 is the zero-order rate constant and is expressed in units of concentration / time [e.g. (mg/ml)/ min).]

or $dC = -k_0\,dt$

Integrating both sides:

$$\int dC = -k_0 \int dt$$

or, $\boxed{C = -k_0 t + C_0.}$ eqn.3

where C_0 is the concentration of drug at t= 0.

Half life of the reaction:

At t = $t_{1/2}$ $C = \frac{1}{2} C_0$.

Replacing t and C in eqn. 3 $\frac{1}{2} C_0. = -k_0 t_{1/2} + C_0$.

or, $k_0 t_{1/2} = \frac{1}{2} C_0$.

or, $\boxed{t_{1/2} = \frac{1}{2}\frac{C_0}{k_0}}$

Unit of k $\dfrac{mg}{ml\ \ min}$

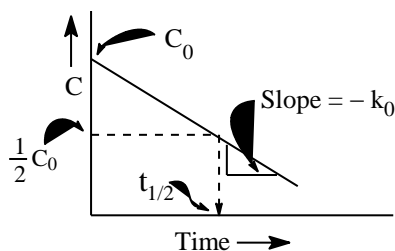Graphical representation

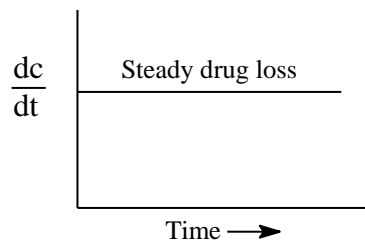Fig: Plot of Conc vs. time   Fig. Rate vs. time

Example
        A drug in suspension follows apparent zero-order kinetics in which the concentration of the drug in the solution remains constant with time. When the drug in the solution degrades or lost by any means new drug molecules from the suspended solid particles dissolve in the solution to keep the concentration constant at the **equilibrium solubility**. That is the solid suspended particles acts as reservoir of drug.

1st Order Reactions
In first order reaction the rate of reaction is proportional to the concentration of the drug remaining and can be expressed as:

$$\frac{dC}{dt} = -kC^1 \quad \text{or simply} \quad \frac{dC}{dt} = -kC$$

$$or, \frac{dC}{C} = -k\,dt \quad \text{........................ eqn 4}$$

Integrating eqn 4 we get,
        ln C = −kt + A where is a constant
Initially when t = 0, C = C_0. Hence, the equation will be

$$\boxed{\ln C = -kt + \ln C_0.} \quad \text{............................ eqn. 5}$$

$$or, \ln\frac{C}{C_0} = -k\,t \qquad or, \frac{C}{C_{.0}} = e^{-kt} \qquad or, \qquad \boxed{C = C_0\,e^{-kt}.} \quad \text{...................... eqn. 6}$$

Another form of eqn. 5 is the expression in $\log_{10}$ format:

$$\boxed{\log C = -\frac{k}{2.303}t + \log C_0.} \qquad \text{... eqn. 7}$$

<u>Half life of the reaction</u>
        At t = $t_{1/2}$ C = $\frac{1}{2}$ C_0.
Replacing t and C in eqn. 7

$$\log \frac{1}{2}C_0 = -\frac{k}{2.303}t_{1/2} + \log C_0.$$

$$or, \quad \frac{k}{2.303}t_{1/2} = \log C_0. - \log\frac{1}{2}C_0.$$

$$or, \quad t_{1/2} = \frac{2.303}{k}\log\frac{C_0}{C_0/2} = \frac{2.303\log 2}{k} = \frac{2.303 \times 0.30103}{k} = \frac{0.693}{k}$$

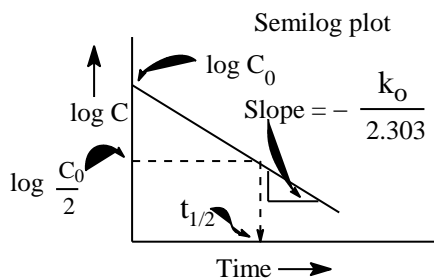$$\boxed{or, t_{1/2} = \frac{0.693}{k}}$$

<u>Graphical representation</u>
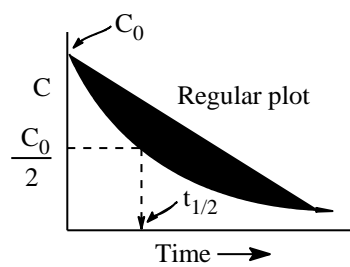

Fig : Plot of eqn. 7   Fig: Plot of eqn.6

<u>Unit of k</u> : min^{-1}.

Example

All the passive transport of drug molecules through the biological membranes follows first order kinetics.
Degradation of hydrogen peroxide into water and oxygen: $2H_2O_2 \rightarrow 2H_2O + O_2$.

INFLUENCE OF TEMPERATURE AND OTHER FACTORS ON REACTION RATE

Influence of temperature

The speed of many reaction increases about two to three times with each 10^0 C rise in temperature. The effect of temperature on a rate constant of a reaction is given by the equation, first suggested by Arrhenius,

$$k = A\,e^{-\frac{Ea}{RT}}$$

in which

k is the specific reaction rate,
A is a constant known as the Arrhenius factor or Frequency factor
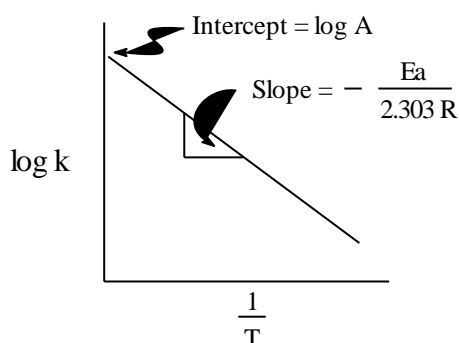**E$_a$** is the energy of activation
R is the universal gas constant
T is the absolute temperature

$$\log k = \log A - \frac{Ea}{2.303\,R}\,\frac{1}{T}$$

A plot of log k vs 1/T yields a
slope equal to $- Ea / 2.303\,R$ from which the value for the energy of activation (Ea) and Arrhenius factor (A) can be calculated.

Intercept = log A

$$\text{Slope} = - \frac{Ea}{2.303\ R}$$

log k

$$\frac{1}{T}$$

So Ea = Slope x 2.303 R
and A = 10 $^{\text{intercept}}$

Influence of light (Photoreaction)

Light energy, like heat, may provide the activation energy necessary for a reaction to occur.
The energy unit of light radiation is *photon* and it is equivalent of 1 *quantum* of energy.
The photochemical reaction rate depends on the *wavelength of light*, *intensity of light* and the *number of photons actually absorbed* by the material.
Examples:
1. Ergosterol, under UV light, transforms into Vitamin D.
2. Oxidation of benzaldehyde by light.
3. Adriamycin, furosemide, menadione, nifedipine, sulfacetamide, theophylline etc. undergoes photodegradation.

Study of photo reactions are required to prepare suitable packaging material for the product e.g. color-glass bottles or paper box or aluminium foil etc.

Influence of solvent

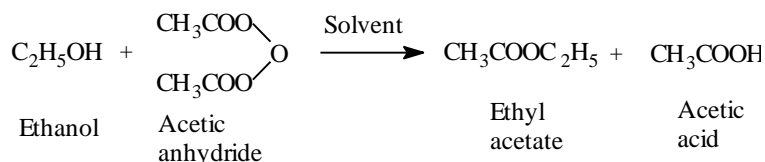Reactant $\xrightarrow{\text{Solvent}}$ Product
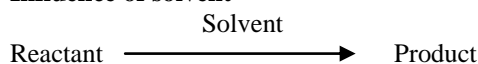
The following facts are found:
If polarity of product > polarity of reactant then reaction rate **increases** if the solvent is **more polar**.
If polarity of product < polarity of reactant then reaction rate **increases** if the solvent is **less polar**.
*Example*:
In this reaction the product (ethylacetate) is less polar than the reactants (ethanol, acetaic anhydride) hence the reaction will be faster in non-polar solvent like hexane, and slower in polar solvent like nitrobenzene.

$$C_2H_5OH + \begin{matrix} CH_3COO \\ \\ CH_3COO \end{matrix}\!\!\!\!\bigg\rangle O \xrightarrow{\text{Solvent}} CH_3COOC_2H_5 + CH_3COOH$$

Ethanol   Acetic anhydride   Ethyl acetate   Acetic acid

Influence of catalytic species
The rate of a reaction is influenced by the presence of a catalyst.

The equilibrium constant of the reaction $K = \dfrac{k_{forward}}{k_{reverse}}$

$$Reactants \underset{k_{reverse}}{\overset{k_{forward}}{\rightleftharpoons}} Product$$
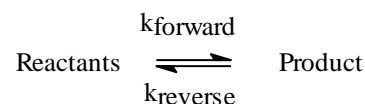
- A catalyst increases both forward and backward reaction rate, hence a catalyst cannot change the equilibrium constant K of the reaction.
- It does not affect the yield of the product also.
- Only it makes the reaction faster.

Catalyst: It is defined as a substance that influences the rate of a reaction but itself remain unchanged chemically.

Negative catalyst: A catalyst that reduces the rate of reaction.
e.g. Phosphoric acid reduces the reaction rate of $H_2O_2 \rightarrow H_2O + O_2$.

Inhibitor: A substance that reduces the rate of reaction and itself gets changed chemically.

Homogeneous catalysis: If the catalyst and the reactants remain in the same phase the process is called homogeneous catalysis.
e.g. Hydrochloric acid catalyses the hydrolysis of sugar.

Heterogeneous catalysis: If the catalyst and the reactants are in separate phases the process is called a heterogeneous catalysis.
e.g. Platinum powder is suspended in reaction medium of hydrogenation reaction.

Catalyst poison: Substances those reduces the action of catalyst are called catalyst poison.
e.g. Copper acts as catalyst in hydrogenation of ethylene. Carbon monoxide acts as poison of copper.

Promoters: Substances those increases the activity of a catalyst are called promoters.
e.g. Ferric ion (Fe^{3+}) acts as catalyst in decomposition of hydrogen peroxide. Cupric ion (Cu^{++}) act as promoter to ferric ion.

ACCELERATED STABILITY STUDY

Accelerated stability testing
Instabilities in modern formulations are often detectable only after considerable storage periods under normal conditions. To reduce the time required to obtain information, various tests that involve storage of the products under conditions that accelerate decomposition have been introduced.
Objectives of accelerated stability tests:
(i) the rapid *detection of deterioration* in different initial formulations of the same product – this is used in selecting the *best formulation* from a series of possible choices;
(ii) the *prediction of shelf life*, which is the time a product will remain satisfactory when stored under expected or directed storage condition; and
(iii) the provision of rapid means of *quality control*, which ensures that no unexpected change has occurred in the stored product.
All these objectives are based on obtaining a more rapid rate of decomposition by applying to the product a storage condition that places a higher stress or challenge to it when compared with normal storage conditions.

Common high stresses or challenges:
(a) Temperature
An increase in temperature causes an increase in the rate of chemical reactions. The products are therefore stored at room temperatures greater than room temperature. The nature of the product often determines the range covered in the accelerated test.
Samples are removed at various time intervals and the extent of decomposition is determined by analysis.
(b) Humidity
Storage of the product in atmospheres of high humidity will accelerate decomposition that result from hydrolysis. Marked acceleration will be obtained if a "naked" product (i.e. not enclosed in a container) is subjected to these tests. This type of stability tests are useful in determining the degree of protection that should be afforded by the container.

(c) Light
A source of artificial light is used to accelerated the effect of sunlight or sky light. the source should emit a similar distribution of radiant energy to that in sunlight because photochemical reactions involve the absorption of light of definite wavelengths.
"Day light" fluorescent lamps provide a satisfactory source.

The prediction of shelf-life:
Say, the room temperature = 25^0C

Method 1: Prediction from Arrhenius plot:
Concentration of undecomposed drug is plotted against time (hr) at various temperature above room temperature (25^0C)
The stability constants at various temperatures are plotted in Arrhenius plot (i.e. log k vs 1/T).
From the Arrhenius plot the stability constant at room temperature i.e. (k_{25}) is determined by extrapolation.

Time in hour

Arrhenius plot
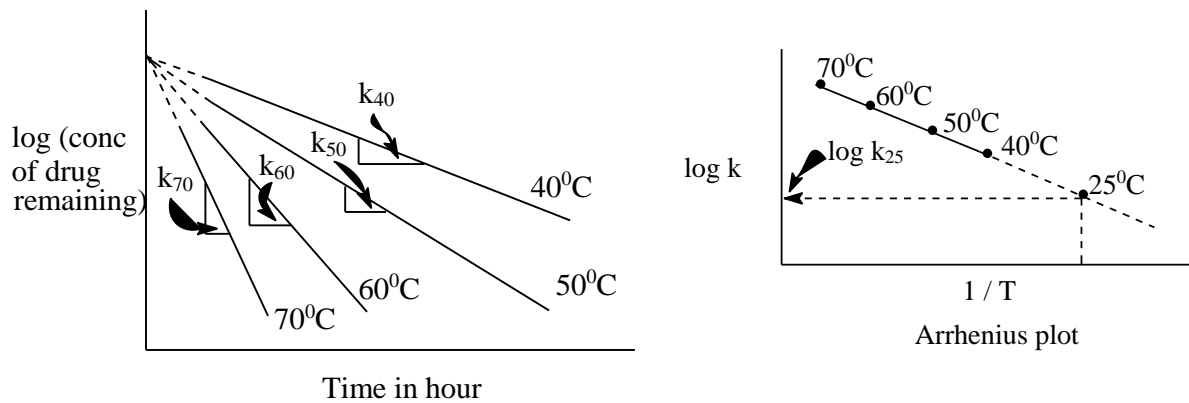
Let us assume that when the drug is 10% decomposed it is to be said that the product has expired.
i.e.   at time t = 0 hour drug concentration remaining = 100%
            at time = t hour   drug concentration remaining = 90%
Now we have to calculate the time 't'.
If the product is kept at room temperature (25^0C)then the following equation from 1st order kinetics may be used:
$$\log C = \log Co - (k_{25}/2.303) \times t$$

or, t   = $(2.303 / k_{25})$
            = $(2.303/k_{25}) \log (Co / C)$
            = $(2.303/k_{25}) \log (100/90)$
Since k_{25} value is known, therefore **t** can be calculated.

Method -II: Simplified techniques for stability prediction:

Free and Blythe describe such technique for liquid products where the decomposition behaves according to the general kinetic laws.

In this case log(% of drug remaining) is plotted against time (in days).

From the graph the time for the potency (concentration) to fall to 90% of the original value (i.e $t_{90\%}$) are read at different temperature.

Then the log ($t_{90\%}$) is plotted against (1/T) and the time at 25^0C gives the shelf life of the product (in days).
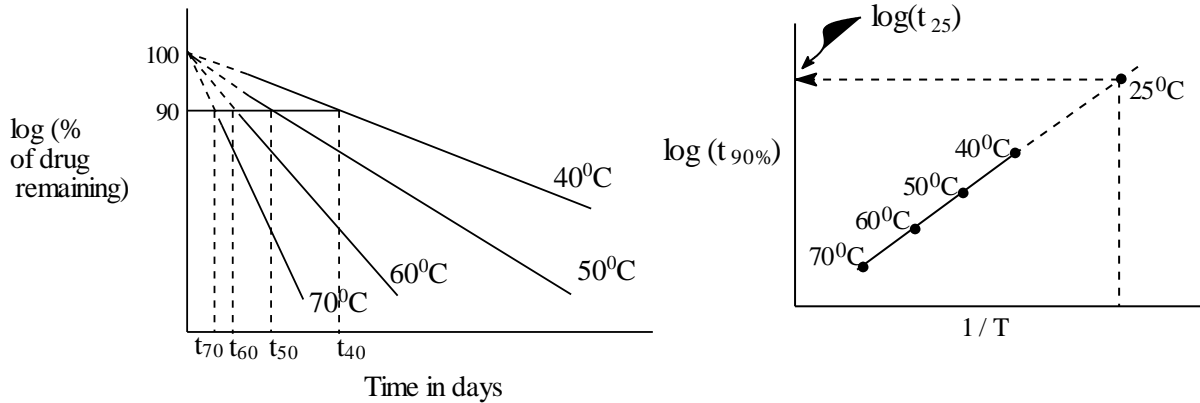
Expiry time = Time required for 90% degradation at room temperature (i.e. 25^0C) = t_{25}.