# CHEMICAL KINETICS AND STABILITY

## STABILITY

The USP defines the stability of pharmaceutical product as "extent to which a product retains within specified limits" and throughout its period of storage and use (i.e its shelf life) the same properties and characteristics that it possessed at the time of its manufacturer"

Stability of drug also can be defined as the time from the date of manufacture and packaging of the formulation until its chemical or predetermined level of labelled potency and its physical characteristics have not changed appreciably.

For a drug substance, we need to study 3 categories of stabilities-

A. Solid state stability of drug only

B. Compatibility studies ( drug+ excipients )

C. Solution phase stability

## CHEMICAL DEGRADATION STUDY

- **Hydrolysis-** usually drugs such as esters, amides and lactams undergo hydrolysis.
- **Oxidation Reduction-** loss of electrons, gain of electrons. Auto oxidation also is responsible. Eg- tetracyclines, vit A, vit D, morphine.
- **Photolysis**- Compounds such as ascorbic acid, riboflavin, cyanacobalamine, folic acid undergo degradation on exposure to light. Sometimes coupled with thermal reactions.
- **Isomerisation**-Compounds get converted into a less effective form. Eg-Adrenaline solutions at low pH lose activity since its levo form is more stable than dextro form

The stability of drug product with time is important in determination of shelf life and expired date.
The stability affected by 3 factors

- Temperature
  High temperature can drive moisture out of a sample and render the material apparently stable otherwise prone to hydrolysis.

- Humidity
  Example- Above 65% relative humidity the beta form of chlortetracycline hydrochloride transforms into alpha form.
- Light.
  e.g. Sodium nitroprusside, nifedipine

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:

$2NO \longrightarrow N2O2$

$N2O2 + O2 \longrightarrow 2NO2$

## 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

$$\text{Rate} = -\frac{d[\text{Reactant}]}{dt} = k[\text{Product}]^a$$

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).

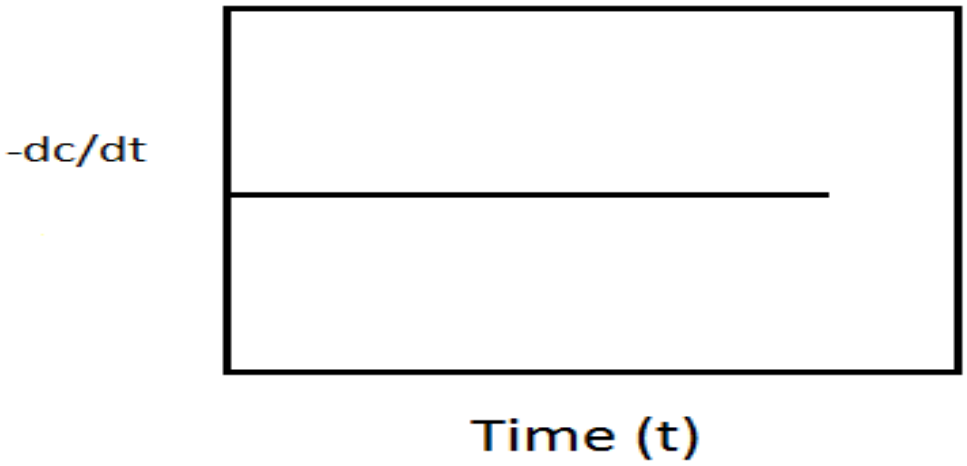
## Kinetic study

## 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

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

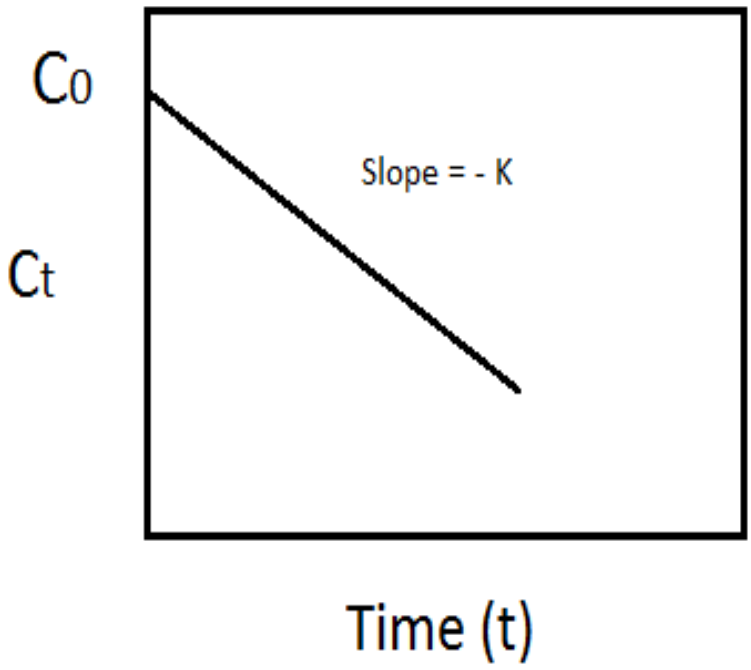
It means that the rate of reaction not depend on concentration of reactant, it is constant with time.




The rate equation can be integrated between the initial concentration, C0, at t = 0, and Ct, the absorbance after time (t):

$$C_t = C_o - k_o t$$

$$t = \frac{C_o - C_t}{k_o}$$



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 1/2Co.

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

$$t_{1/2} = \frac{½Co}{ko}$$

For shelf life $$t_{10\%} = \frac{C0 - 0.9C0}{K_0}$$

The unit of zero order rate constant is:

$$K_0 = -\frac{dc}{dt} = \frac{\text{mole/liter}}{\text{second}} = \frac{\text{mole}}{\text{liter second}} = \text{mole liter}^{-1}\ \text{second}^{-1}$$

**Reference text: Physical Pharmacy by Alfred Martin et al.**