

6.2.2.2. Solvent

The effect of solvents on the degradation rate of drugs is generally related to the relative solubility of the reactants and the products in the given solvents.

For a reaction:



The quantitative relationship between the reaction rate constant and the solubility of the reactants and products is given by the equation.

$$\log k = \log k_0 + \frac{V}{2.303R} \cdot \frac{1}{T} (\Delta\delta_A + \Delta\delta_B - \Delta\delta^*)$$

Where,

k = Observed reaction rate constant.

k_0 = Reaction rate constant in an infinitely dilute solution exhibiting ideal behaviour.

V = Approximation for the molar volumes of the reactants (A and B) and the activated complex formed during the reaction and prior to the formation of the products.

δ_A , δ_B , and δ^* = Solubility parameters of the reactants A, B, and the activated complex, respectively.

On the basis of the above equation, it can be said that polar solvents tend to accelerate reactions in which the products formed are more polar than the reactants. On the other hand, if the products formed are less polar than the reactants, the reaction proceeds better in solvent of relatively low polarity.

Commonly used non-aqueous solvents for drugs include ethanol, glycerol, propylene glycol, polyethylene glycols, and vegetable oils.

6.2.2.3. Ionic Strength

The effect of ionic strength of a solution of the degradation rate may be expressed in the form of the following equation:

$$\log k = \log k_0 + 1.02 Z_A Z_B \sqrt{\mu}$$

Where,

k = Degradation rate constant for the reaction.

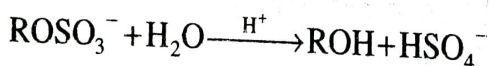
k_0 = Reaction rate constant at infinite dilution.

Z_A and Z_B = Charges carried by the reactants A and B in solution.

μ = Ionic strength of the solution.

According to the above equation, an increase in the ionic strength of the solution would decrease the rate of reaction involving interaction between oppositely charged ions and increase the rate of reaction between similarly charged ions.

For example, the hydrogen ion-catalysed hydrolysis of sulphate ester would be inhibited by an increase in the electrolyte concentration.



Reaction between ions and dipolar molecules and reaction between neutral molecules are not affected to a significant extent by change in ionic concentration. Reactions which result forms oppositely charged ions (as products) exhibit an increase in reaction rate on increasing the ionic strength.

6.2.2.4. Dielectric Constant

The dielectric constant of the solvent has a significant effect on the rate of reaction. For a reaction involving a charged reactant molecule and another ionic

species (such as H^+ or OH^-), the effect of dielectric constant on the reaction rate is given by the equation:

$$\ln k = \ln k_{\epsilon = \infty} - \frac{NZ_A Z_B e^2}{RT r^*} \frac{1}{\epsilon}$$

Where,

k = Observed reaction rate in a solvent of dielectric constant (ϵ).

$k_{\epsilon = \infty}$ = Reaction rate constant in a solvent of infinite dielectric constant.

N = Avogadro's number.

Z_A and Z_B = Charges on the two ionic species.

e = Unit of electric charge.

r^* = Distance between the ionic species in the activated complex.

ϵ = Dielectric constant of the solution.

According to the above equation, reactions involving ions of opposite charge are accelerated by solvents of low dielectric constant. **For example**, the rate of H^+ ion catalysed-hydrolysis of sulphate esters is much greater in low dielectric solvents such as methylene chloride than in water.

On the other hand, in reactions involving similarly charged species, the rate of reaction is accelerated on increasing the dielectric constant of the solvent. Reactions between neutral molecules which produce a highly polar transition state are also enhanced by high dielectric constant solvents.