CHAPTER II

REVIEW of LITERATURE

Piroxicam

In formulation of parenteral drug solution, the solubility of a drug is the most important since the drug must be completely dissolved in its vehicles. Piroxicam is not soluble in water and cyclohexane. It is sparingly soluble in diisopropyl ether and in toluene, and only slightly soluble in lower aliphatic alcohols, methanol, ethanol and isopropanol. It is soluble in some polar organic solvents such as dimethyl formamide (1 g/10 ml), dimethyl-sulfoxide (1 g/10 ml), chloroform (1 g/20 ml), and somewhat less soluble in dioxane (1 g/40 ml) and ethyl acetate (1 g /80 ml) (Florey, 1972).

Tsai Hsu and Naito,(1984) determined the solubility of piroxicam in phosphate buffer pH 2-10 as shown in Figure 1. The results showed that solubility of piroxicam increased as the pH increased. Piroxicam has two intramolecular hydrogen bonds which are formed by internal rotation of the neutral structure between enolate oxygen and hydrogen on amide nitrogen and between carbonyl oxygen and hydrogen on pyridine nitrogen. There is no data about the use of cosolvents to increase the solubilities of piroxicam.

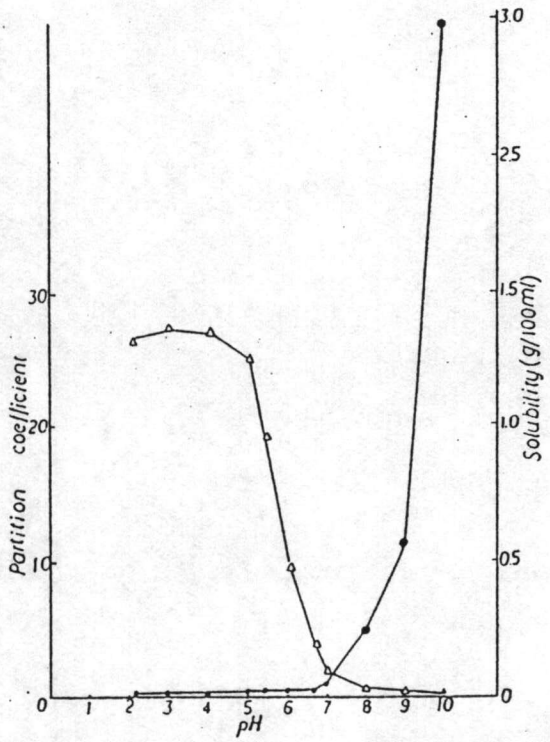

Figure 1 : Relationship between partition coefficient (Δ) and solubility of piroxicam (●) in various pH-buffered solutions

Increasing solubilities of normally insoluble or poorly soluble drug by complexation has been advanced. (Yalkowsky, 1981). A complex is an entity formed when two molecules, such as a drug and solubilizing agent (ligand), are held together with weak forces. Application to a parenteral formulation was demonstrated when the apparent solubility of hexamethylmelamine was increased as much as 90-fold via complexation with gentisate ion (Kreilgard, Higuchi and Repta, 1975).

Nicotinamide is a nontoxic vitamin that has been shown to enhance the aqueous solubilities of many drugs through complexation. For example, Hata, Mizuno and Tomio (1970) studied the solubility enhancement of menadione by complex formation with nicotinamide and other compounds; they explained the complex formation as the result of a Pi donor-Pi acceptor interaction. Using molecular orbital calculations, Fawzi, Davison and Tute (1980) showed that the complexation species of certain heteroaromatic drug molecules with nicotinamide occurs via a Pi donor-Pi acceptor mechanism. Hamza and Paruta (1985) reported that Nicotinamide 40% W/V increased solubility of paracetamol to 15 fold. Harte and Chen (1979) reported about increasing solubility of riboflavin and tryptophan can be done in nicotinamide solution.

Truelove et al (1984) showed that nicotinamide also increased the solubility of erythro-9 (2-hydroxy-3-nonyl) adenine (NSC 263164), the anti-cancer agents, and the

solubilities depended on the pH. The use of cosolvent (20% ethanol) reduces the amount of nicotinamide required to achieve the desired solubility by a factor of 2.

Another study is that of Rasool, Hussain and Dittert (1991) showed that the solubilities of five poorly water-soluble drugs were found to be increased in a non linear fashion as a function of nicotinamide concentration. More details about cosolvent and complexation method to increase solubilities will be stated.

The stabilities of piroxicam

Piroxicam is very stable when kept at 20°C to 40°C or after irradiated with light (Florey, 1972). Fini and Rabasco (1992) studied the stability of piroxicam in aqueous solution as a function of pH. UV absorbance at 350 nm of piroxicam solutions was changed during two hours. This change is less rapid at low and high pH values (Figure 2)

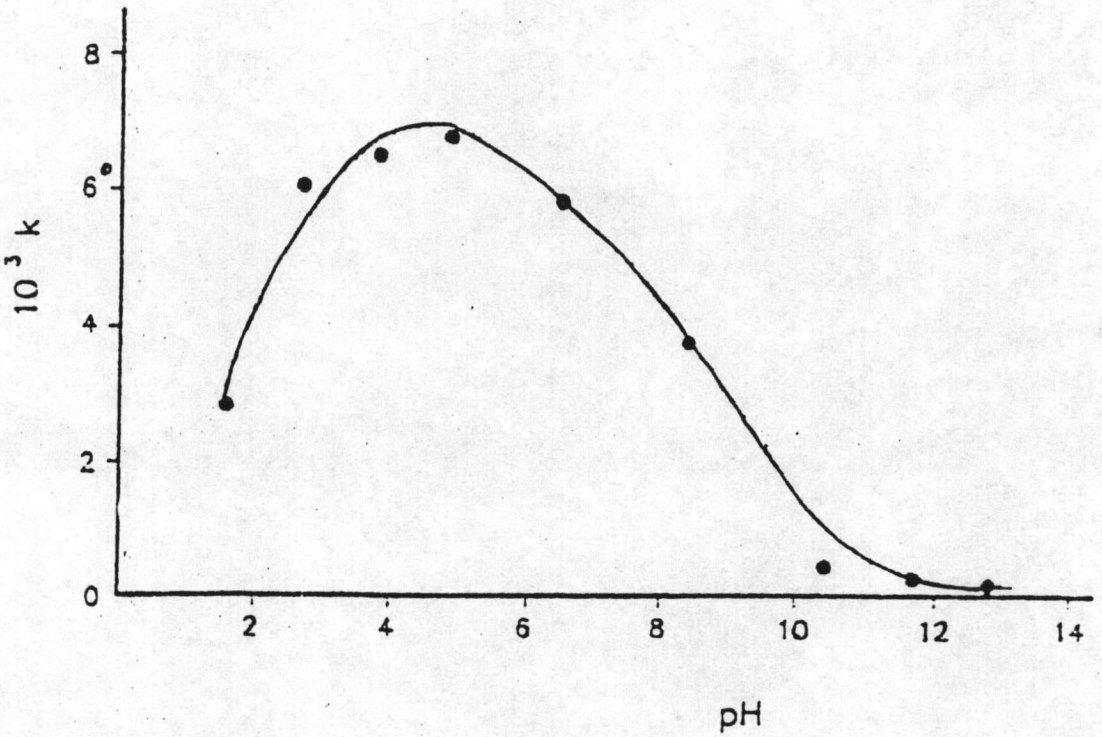

Figure 2 : Absorbance change rates as a function of pH

Drug Solubilization Technique

1. Drug solubilization by cosolvents

Cosolvents are defined as water-miscible organic solvents that are used in liquid drug formulations to increase the solubility of poorly water-soluble substances or to enhance the chemical stability of drug. (Yalkowsky, 1981; Avis, Lachman and Lieberman, 1984). When used for the purpose of increasing the solubility of drugs, cosolvency compares with other methods as being among the most potent. (Swarbrick and Boyland, 1990). Table 1 presents a comparison of the magnitudes of increases in solubility that can be expected from commonly used methods of drug solubilization. Cosolvents were used in some commercially available products. (Yalkowsky, 1981) as seen in Table 2.

When used as a method for increasing the chemical stability of a drug, cosolvents may be effective by one or two mechanisms. If a drug is subject to hydrolytic degradation, cosolvent may reduce the degradation of the drug by reducing the concentration of water in the formulation. Alternatively, a cosolvent may enhance the stability of a drug by providing a less suitable environment for the transition state of the reactants, providing the transition state is more polar than the reactants themselves (Connors, Amidon and Kennon, 1986). Table 3 presents a list of cosolvents commonly used in drug formulation.

Table 1 : Comparison of drug solubilization techniques (Swarbrick and Boyland, 1990)

Method	Approximate Range of Solubility Increase
Cosolvency	1-1000 X
Salt formation	1-1000 X
Prodrug formation	1-1000 X
Complexation	1-100 X
Micellization	1-50 X

Table 2 : Some parenteral products containing cosolvents (Avis, Lachman, and Lieberman, 1984)

Trade name	Manufacturer	General name	Cosolvent composition
Dramamine	Searle	Dimenhydrinate	50% propylene glycol
Apresoline	Ciba	Hydralazine HCl	10% propylene glycol
MVI	USV	Multivitamin infusion	30% propylene glycol
Nembutal	Abbott	Phenobarbital sodium	10% ethanol, 40% propylene glycol
Luminal	Winthrop	Pentobarbital sodium	67.8% propylene glycol
Dilantin	Parke-Davis	Phenytoin sodium	10% ethanol, 40% propylene glycol
DHE 45	Sandoz	Dihydroergotamine mesylate	6.1% ethanol, 15% glycerin
Cedilanid	Sandoz	Deslanoside	9.8% ethanol, 15% glycerin
Robaxin	Robbins	Methocarbamol	50% polyethylene glycol
Serpasil	Ciba	Reserpine	10% dimethylacetamide, 50% polyethylene glycol
Ativan	Wyeth	Lorazepam	80% propylene glycol, 20% polyethylene glycol
Librium	Roche	Chlordiazepoxide	20% propylene glycol
Valium	Roche	Diazepam	10% ethanol, 40% propylene glycol
Lanoxin	Burroughs Wellcome	Digoxin	10% ethanol, 40% propylene glycol

Table 3 : Cosolvents used in drug formulations

(Swarbrick and Boyland, 1990)

Cosolvent	Dielectric Constant* (E)	Solubility Parameter (S) $(cal/cm^3)^{1/2}$	Interfacial Tension+ (dynes/cm)
Water	78.5	23.4	45.6
Glycerin	42.5	17.7	32.7
N,N-Dimethyl-acetamide	37.8	10.8	4.6
Propylene glycol	32.0 (30°)	12.6	12.4
Ethanol	24.3	12.7	0.5
Polyethylene glycol 400	13.6	11.3	11.7
Dimethylisosorbide	-	8.63	4.2

*All values determined at 25°C unless stated otherwise.

+Determined against liquid paraffin..

2. Drug solubilization by complexing agent

A complex is a species of definite substrate (Active ingredient) to ligand (complexing agent) stoichiometry which can be formed in an equilibrium process, in solution and also may exist in the solid state. (Zografi, 1990; Martin, Swarbrick and Cammarata, 1993)

Type of phase solubility diagrams

A phase diagram is constructed by plotting, on the vertical axis, total molar concentration of substrate (s) found in the solution phase against the molar concentration of ligand added to the system. The phase diagrams are observed to fall into two main classes, with some variation within the classes.

A. Type A diagrams

Type A diagrams indicate the formation of soluble complexes between substrate and ligand, thereby in creasing the total amount of substrate (s) in solution, and does not form a precipitated regardless of the amount of ligand added. (Yalkosky, 1981)

The A_L diagram is obtained when the complex has a first order dependence on (L) t. which exhibited a linear relationship between St and Lt (Figure 3)

The A_P diagram, a positive deviation from linearity, is obtained when the complexes formed contain more than one molecule of ligand.

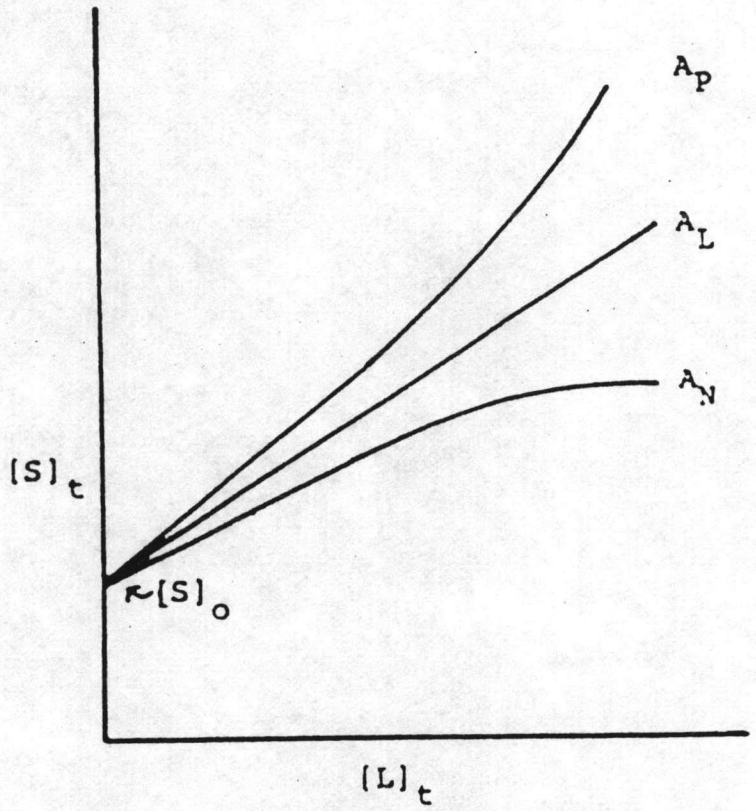

Figure 3 : The type A phase diagrams.

The A_N diagram, a negative deviation which presented a decreasing dependence on ligand added at higher ligand concentrations.

B. Type B diagrams

Type B diagrams, are observed when insoluble complexes are formed which results in the developing of third phase. (Figure 4)

The B_S diagram shows an initial rise in substrate concentration.

The B_I diagram shows that the complex was insignificantly soluble relative to the inherent solubility of the substrate.

In the B- system diagram, the plateau region represents solution compositions which were invariant due to formation and precipitation of the complex. The decrease in substrate following the plateau is due to the disappearance of any undissolved substrate.

Stability study

A study of kinetic of degradative reactions in the pharmaceutical formulation is determined at a definite rate which the drug is decomposed (Connors, Amidon and Kennon, 1986).

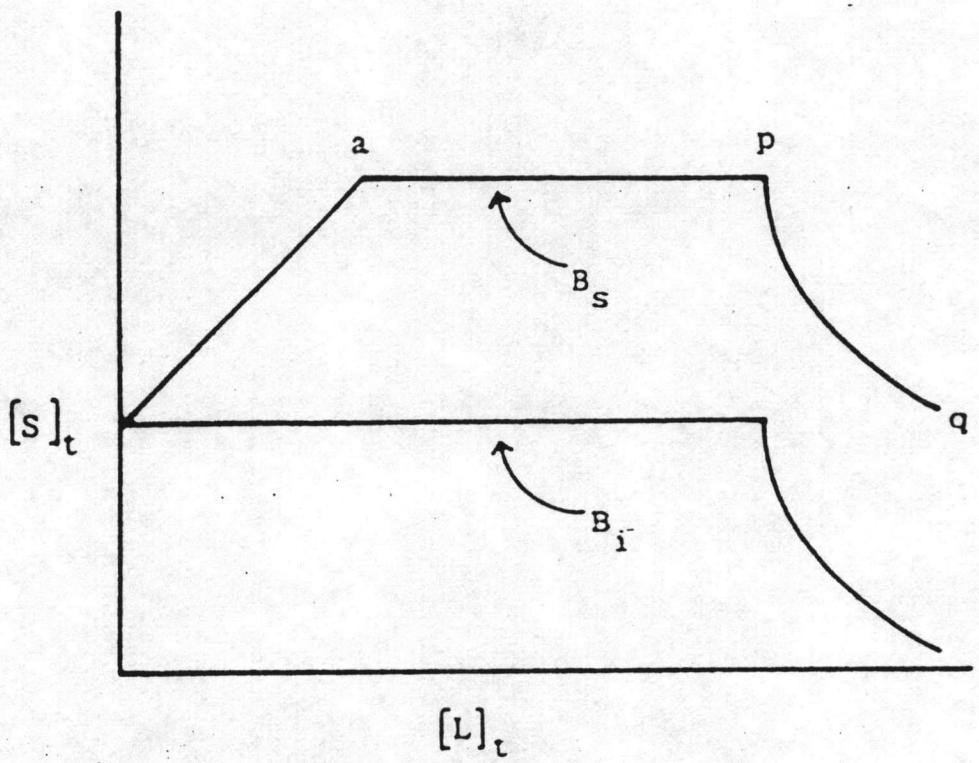

Figure 4 : The type B phase diagrams.

1. Rate of reaction

The rate of a reaction can be expressed either as the increase (+) or decrease (-) of concentration within a given time interval. The rate of the reaction may be written as $-d[D]/dt$ or $d[P]/dt$ where D is a drug molecule and P is a product molecule.

1.1 Order of reaction

The order of a chemical reaction determines the shape of the concentration-time profile of a drug or a drug product, whereas the rate constant determines its slope.

1.1.1 Zero order calculations

A zero order reaction is one having a rate equation of the form of Eq (1), that is, with no concentration dependence.

$$\frac{-d[D]}{dt} = k_o \qquad \text{Eq.1}$$

Integrating from t = 0 to t = t with $[D] = [D]_o$ at t = 0 yields

$$[D] = [D]_o - k_o t \qquad \text{Eq.2}$$

Hence for a zero-order reaction, a plot of concentration against time is linear (Figure 5). with a slope of k_o. The units of k_o are concentration/time.

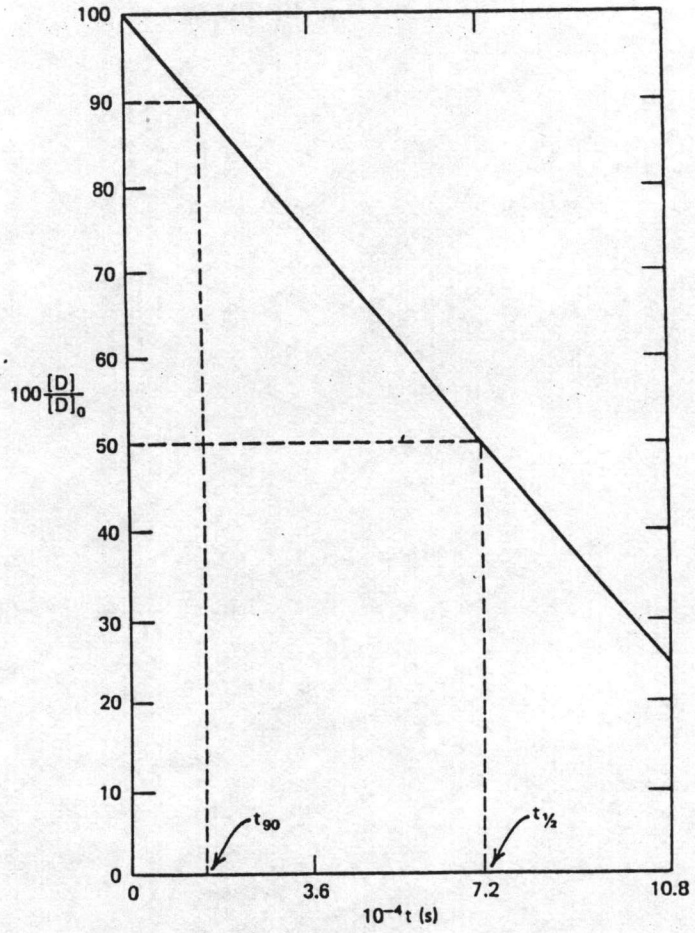

Figure 5 : Percent of drug remaining as a function of time for a zero-order reaction.

The half-life and shelf-life are calculated by the following equations.

$$t_{1/2} = \frac{0.5[D]_o}{k_o} \qquad \text{Eq.3}$$

$$t_{90} = \frac{0.1[D]_o}{k_o} \qquad \text{Eq.4}$$

1.1.2 First-Order calculations

A typical first-order reaction may be written as

$$D \xrightarrow{k_1} \text{products}$$

and its corresponding rate equation as

$$-\frac{d[D]}{dt} = k_1 [D]_o \qquad \text{Eq.5}$$

This expression defines the rate of the reaction whereas it is actually needed to know the concentration-time profile. This is obtained by integrating the rate from t = 0 to t = t, where [D] at t = 0 is $[D]_o$

$$\ln [D] = \ln [D]_o - k_1 t \qquad \text{Eq.6}$$

Alternative forms of this equation are

$$[D] = [D]_o \, e^{-k_1 t} \qquad \text{Eq.7}$$

and

$$\log [D] = \log [D]_o - \frac{k_1 t}{2.303} \qquad \text{Eq.8}$$

Thus a plot of log [drug concentration] against time will be linear with the slope equal to $-k_1/2.303$, yielding the rate constant (Figure 6). The half-life, $t_{1/2}$, is the time for [D] to become $[D]_o/2$. An equation for $t_{1/2}$ is

$$\ln[D]_o/2 = \ln[D]_o - k_1 t_{1/2} \qquad \text{Eq.9}$$

$$\frac{\ln 2}{k_1} = t_{1/2} \qquad \text{Eq.10}$$

$$t_{1/2} = \frac{0.693}{k_1} \qquad \text{Eq.11}$$

The shelf-life, t_{90}, of a drug will be taken to be the time for [D] to reach $0.90[D]_o$. An equation for t_{90} is

$$t_{90} = \frac{0.105}{k_1} \qquad \text{Eq.12}$$

Figures 6 and 7 show the relationship of these quantities graphically.

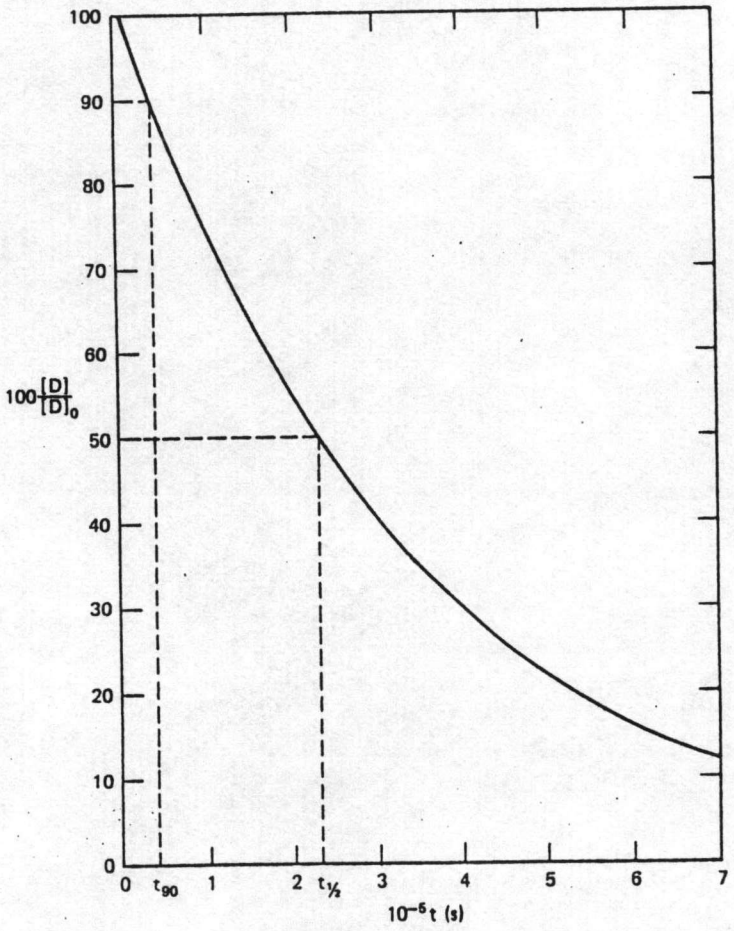

Figure 6 : Percent of drug remaining as a function of time for a first-order reaction.

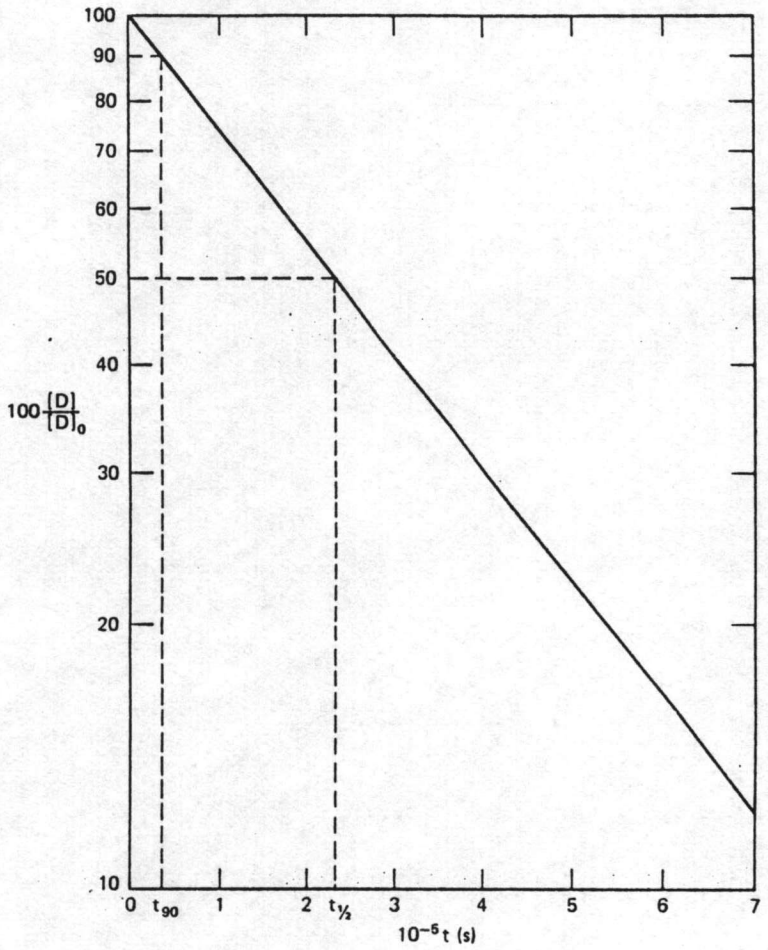

Figure 7 : Log (precent of drug remaining) as a fuction of time for a first-order reaction.

2. Temperature effects

Activation-energy calculations

Reaction rates are expected to be proportional to the number of collisions per unit time. Since the number of collisions increases as the temperature increases. It would expect the reaction rate increase with increasing temperature. Experimentally, the reaction-rate constant is observed to have an exponential dependence on temperature :

$$k = Ae^{(-Ea/RT)} \qquad \text{Eq.13}$$

Where k is the reaction rate constant of any order, A is frequency factor, Ea is the energy of activation, R is the gas constant, 1.987 calories/deg mole, and T is the absolute temperature. This equation is called the Arrhenius equation that can be written in several equivalent forms as follows :

$$\log k = \log A - Ea/2.303\ RT \qquad \text{Eq.14}$$

$$\log\left[\frac{k_2}{k_1}\right] = \frac{-Ea}{2.303R}\left[\frac{1}{T_2} - \frac{1}{T_1}\right] \qquad \text{Eq.15}$$

$$\log\left[\frac{k_2}{k_1}\right] = \frac{Ea\ (T_2 - T_1)}{2.303\ R\ T_1 T_2} \qquad \text{Eq.16}$$

Where k_2 and k_1 are the rate constants at temperature T_2 and T_1, respectively. The interpretation of Ea is as follow : as the reaction proceeds from reactants to

products the system must pass through a state whose energy is greater than that of the initial reactants (Figure 8). This "barrier" is what prevents the reactants from immediately becoming products; the activation energy is a measure of this barrier.

Equation 14 indicates that a graph of log k against 1/T will be linear with a slope of -Ea/(R 2.303). This type of graph is called an Arrhenius plot. From this plot A and Ea can be determined. (Figure 9)

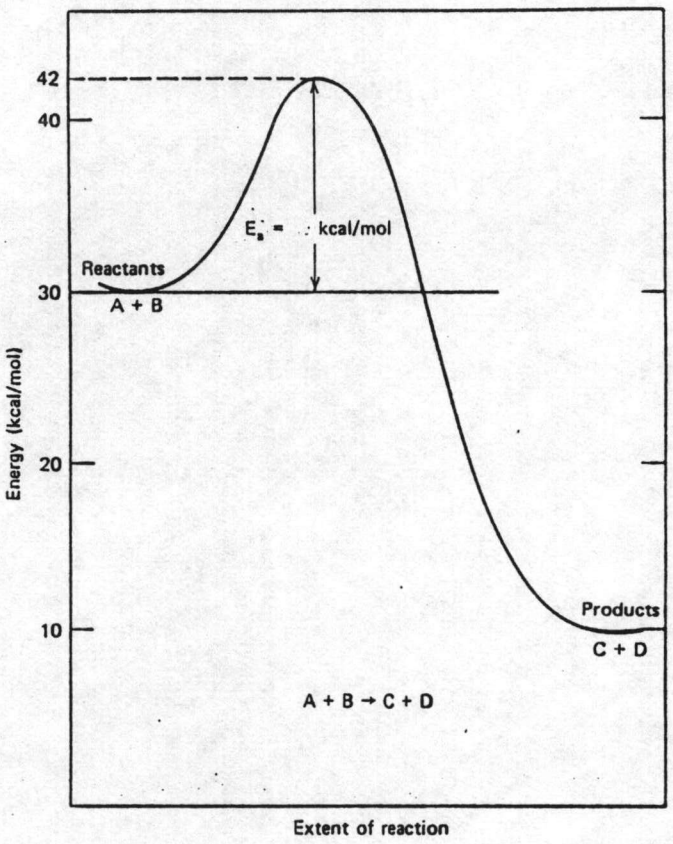

Figure 8: Schematic representation of how the energy of the system may be changed.

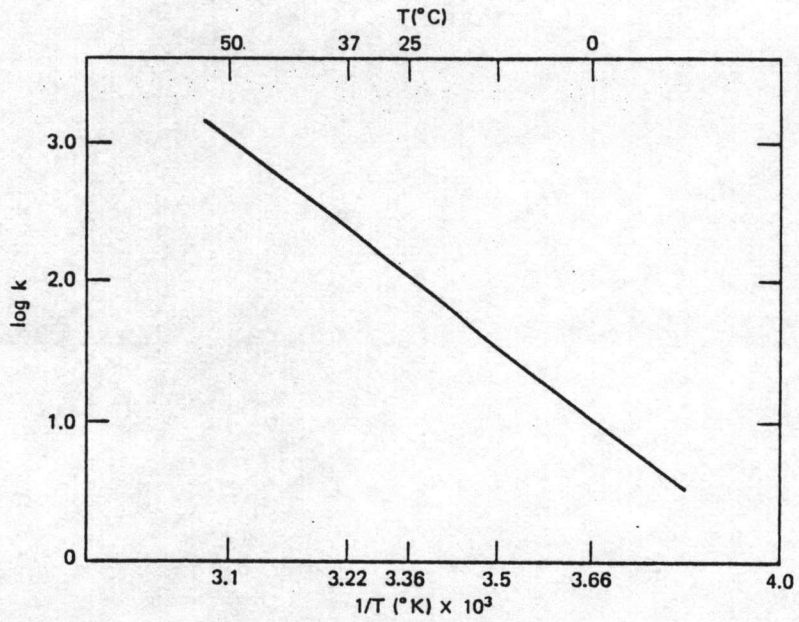

Figure 9: Typical Arrhenius plot of log k against 1/T, according to equation 14.