CHAPTER II

REVEIW OF LITERATURE

Solubility of Indomethacin

In formulation of drug solutions, the solulibity data of the drugs are important since the drugs must dissolve completely in their vehicles. Indomethacin is practically insoluble in water but soluble in alcohol, chloroform, ether and acetone. It is also soluble in alkaline solutions but with decomposition (Reynolds, 1982). Solubility of indomethacin had been studied in various mixed solvents (Patcharin, 1985). Its solubility was also improved by micellar solubilization (Lin and Kawashima, 1985). Increasing solubility of normally insoluble or poorly soluble drugs by surface active agents has been an advance in many pharmaceutical products (Zografi, Swarbrick and Schott, 1990). Micellar solubilization in water can be classified into the following three types: a) the solubilizate is adsorbed onto the micelle surface; b) the solubilizate is embeded in the hydrocarbon interior of micelle; c) the solubilizate is included within the palisade region of hydrophilic chains (Attwood and Florence, 1983). Many nonionic surfactants have been widely used in the pharmaceutical industry because they are less toxic to

biological systems than other cationic or anionic surfactants, and a smaller concentration is required due to their low CMC (critical micelle concentration) value (Mulley, 1964).

Micellar solubilization of indomethacin was studied in aqueous solutions of pluronic F68, pluronic F88, and pluronic F108 (Lin and Kawashima, 1985), pluronic F127 (Tomida, Kuwada and Kiryu, 1988) and polysorbate 80 (Krasowska, 1979). The pluronics are poly(oxyethylene) poly(oxypropylene)poly(oxyethylene) block copolymers which received interest for use in the formulation of dosage forms owing to their low toxicity and ability to form a clear solution or gel in aqueous media. The apparent solubilities of indomethacin in the study are increased with the increase of the concentrations of surfactants.

Percutaneous Absorption of Indomethacin

Naito and Tsai (1981) studied the percutaneous penetration of indomethacin through ointment bases. The ointments were solution-type and suspension-type. The solution-type ointments were ointments that contained dissolved indomethacin while the suspension-type ointments were suspended with the fine powder of the drug. Indomethacin was more effectively absorbed from the solution-type ointments than from the suspension-type ointments.

The percutaneous penetration of indomethacin in a

gel base containing water, ethanol, propylene glycol and carbopol is significant. The indomethacin concentration in the skin at the applied sites were greater than that at the non applied sites (Ishihama, Kimata and Mizushima, 1979). A later related work studied on antiinflammatory activity of indomethacin gel showed that the indomethacin gel produced significant inhibitory effects and the activity was approximately equivalent to or more effective than that of the placebo ointment (table 1) (Wada, 1982).

Stability study

A study of the reaction kinetics of decomposition enables a quantitative assessment to be made of the rate at which the drug is destroyed (Connors, Amidon and Kennon, 1979).

1. Rate of Reaction

The rate of a reaction can be expressed either as the decrease in concentration per unit time of any of the reacting substances, or as the increase in concentration per unit time of one of the products. The rate of reaction may be written as $-\frac{d[D]}{dt}$ or $\frac{d[P]}{dt}$ where D is a drug molecule and P is a product molecule.

1.1 Order of reaction Order of reaction expresses the experimentally determined dependence of the rate upon the reactant concentrations. The order of

Table 1 : Dose response of indomethacin ointments applied topically on carrageenan-induced oedema in rats

sample		Oedema weight[a] (g)	Inhibition (%)
placebo ointment		0.64±0.04	
Indomethacin gel	0.3 %	0.61±0.03	4.7
	1.0 %	0.52±0.03	18.8
	3.0 %	0.39±0.02	39.1

[a] Each value indicates the mean ± s.d. of 12 rats.

reaction with respect to a single reactant is equal to the power to which the concentration term of the reactant is raised in the experimental rate equation. For example, a chemical reaction can be expressed as

$$uA + vB + wC \xrightarrow{k} \text{products} \qquad (1)$$

and if its reaction rate is

$$\text{rate} = k[A]^u [B]^v [C]^w \qquad (2)$$

where A, B and C are the ractants and k is a rate constant; u, v and w will be the order of reaction. If u, v and w have values of 2, 1 and 0, respectively, it is said to be second-order with respect to A, first-order in B and zero-order in C. In this instance, the experimentally determined rate is only dependent upon the concentrations of reactants A and B. The overall order of reaction is the sum of the powers of the concentration terms affecting the experimentally determined rate. In the above example, the reaction would be third-order overall.

1.1.1 First-order calculations

A typical first-order reaction may be written as

$$D \xrightarrow{k_1} \text{products} \qquad (3)$$

and its corresponding rate equation as

$$-\frac{d[D]}{dt} = k_1 [D] \qquad (4)$$

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 $[D]_0$ and [D] at any time t is [D].

$$\ln [D] = \ln [D]_0 - k_1 t \quad (5)$$

Alternative forms of this equation are

$$[D] = [D]_0 e^{-k_1 t} \quad (6)$$

and

$$\log [D] = \log [D]_0 - \frac{k_1 t}{2.303} \quad (7)$$

Figure 1 shows a concentration-time profile of a first-order degrading drug. A plot of log [drug concentration] against time would be linear with a slope of $-k_1/2.303$ (figure 2) and the rate constant, k_1, can be therefore calculated. The dimension of k_1 is 1/time, for example, s^{-1}. The half-life, $t_{1/2}$, is the time for [D] to become $[D]_0/2$, that is, one-half the original concentration. An equation for $t_{1/2}$ is found by substituting $[D] = [D]_0/2$ into equation (5).

$$t_{1/2} = \frac{0.693}{k_1} \quad (8)$$

The shelf-life, $t_{0.9}$, of a drug will be taken to be the time for [D] to reach 0.90 $[D]_0$, that is, 10 %

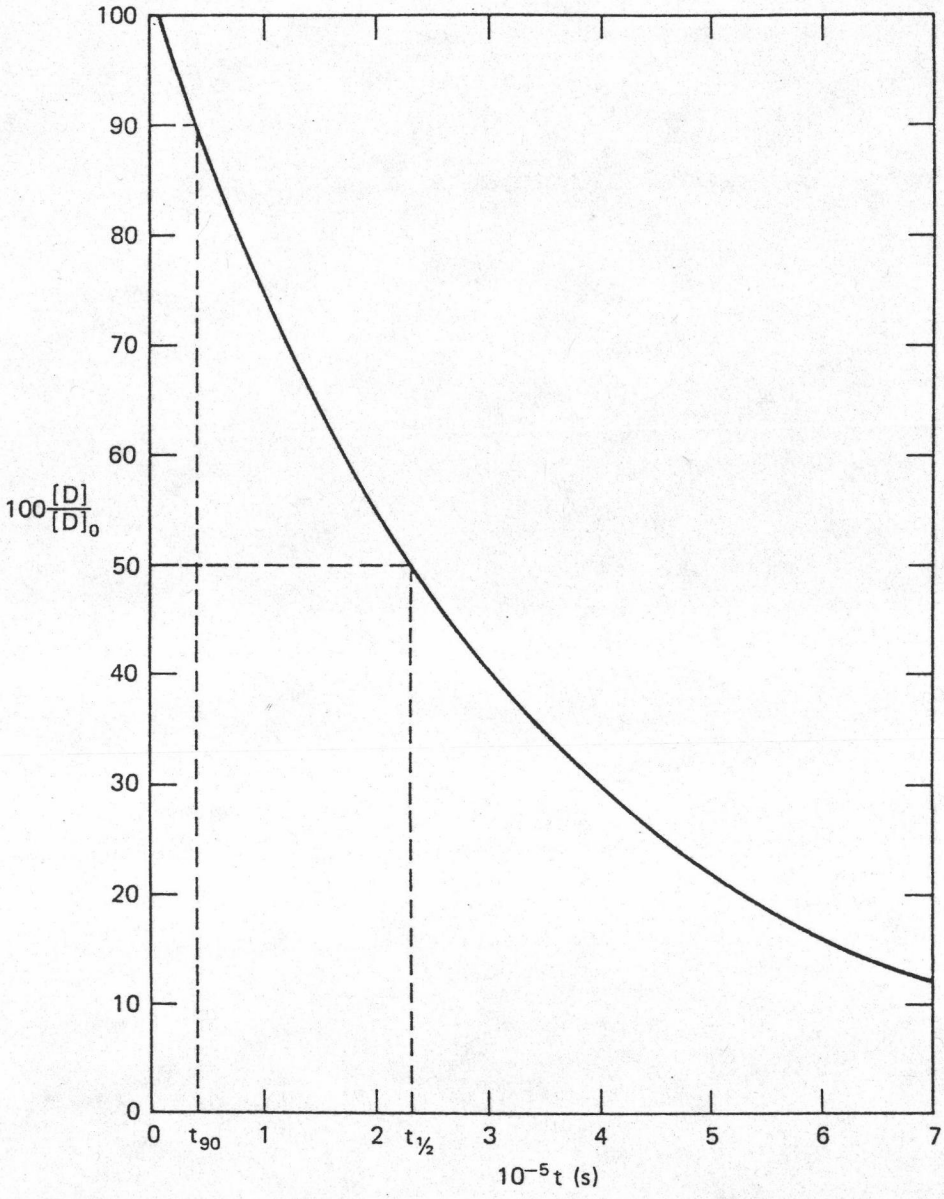


Figure 1. Percent of drug remaininng as a function of time for a first-order reaction.

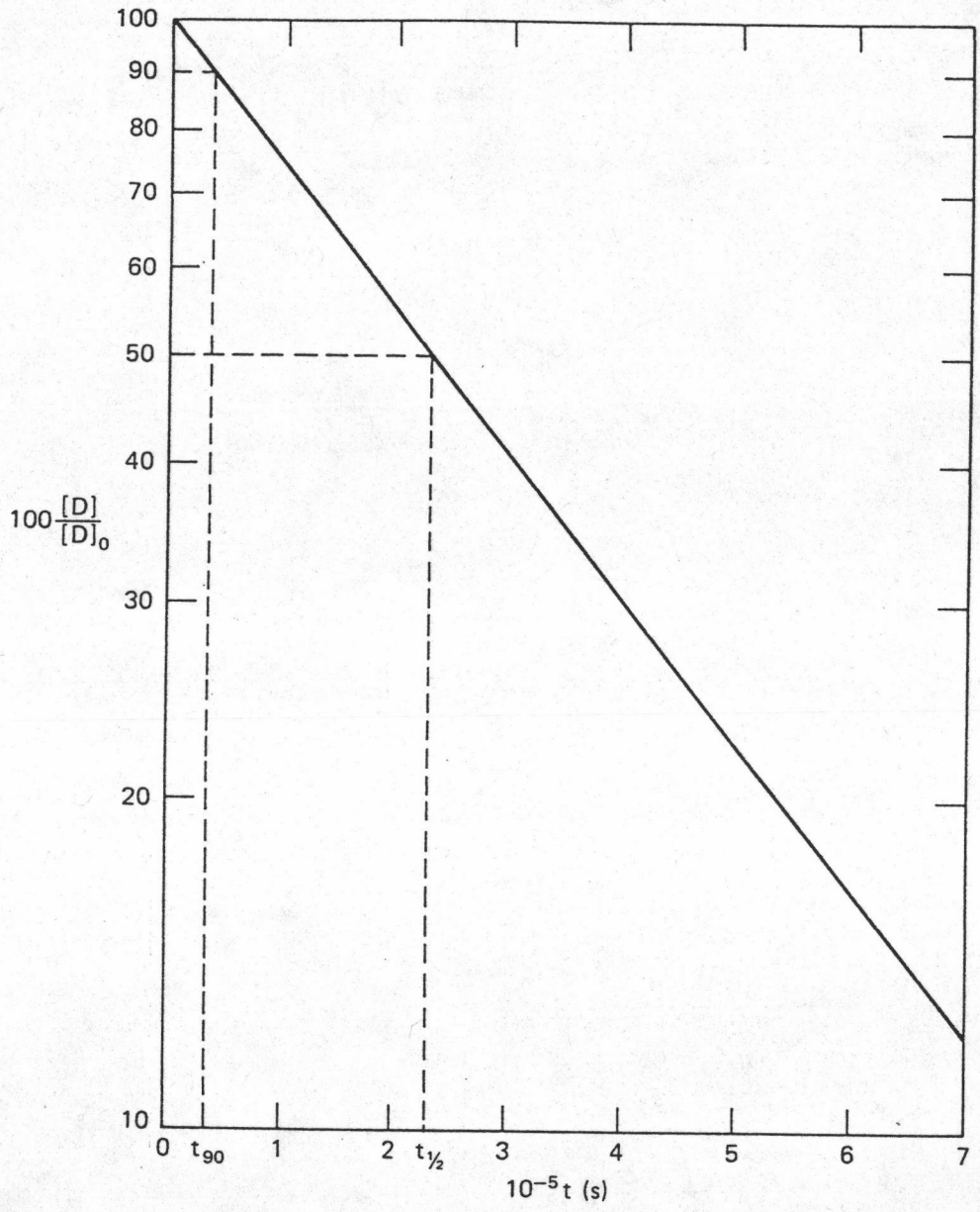


Figure 2. Log (percent of drug remaining) as a function of time for a first-order reaction.

decomposition, so in a similar way it is found that

$$t_{0.9} = \frac{0.105}{k_1} \quad (9)$$

Figures 1 and 2 show the relationship of these quantities graphically.

1.1.2 Zero-order calculations A zero-order reaction is the one having a rate equation of the form,

$$-\frac{d[D]}{dt} = k_0 \quad (10)$$

The zero-order reaction has no concentration dependence. Integrating equation (10) from t = 0 to t = t with $[D] = [D]_0$ at t = 0, and [D] = [D] at any time t yields

$$[D] = [D]_0 - k_0 t \quad (11)$$

Hence, for a zero-order reaction, a plot of concentration against time is linear (figure 3), with a slope of k_0. The units of k_0 are concentration/time, for example, $M.s^{-1}$ when [D] is expressed in molar units. The half life and shelf life are, respectively,

$$t_{1/2} = \frac{0.5\,[D]_0}{k_0} \quad (12)$$

$$t_{0.9} = \frac{0.1\,[D]_0}{k_0} \quad (13)$$

These relationships are shown in figure 3.

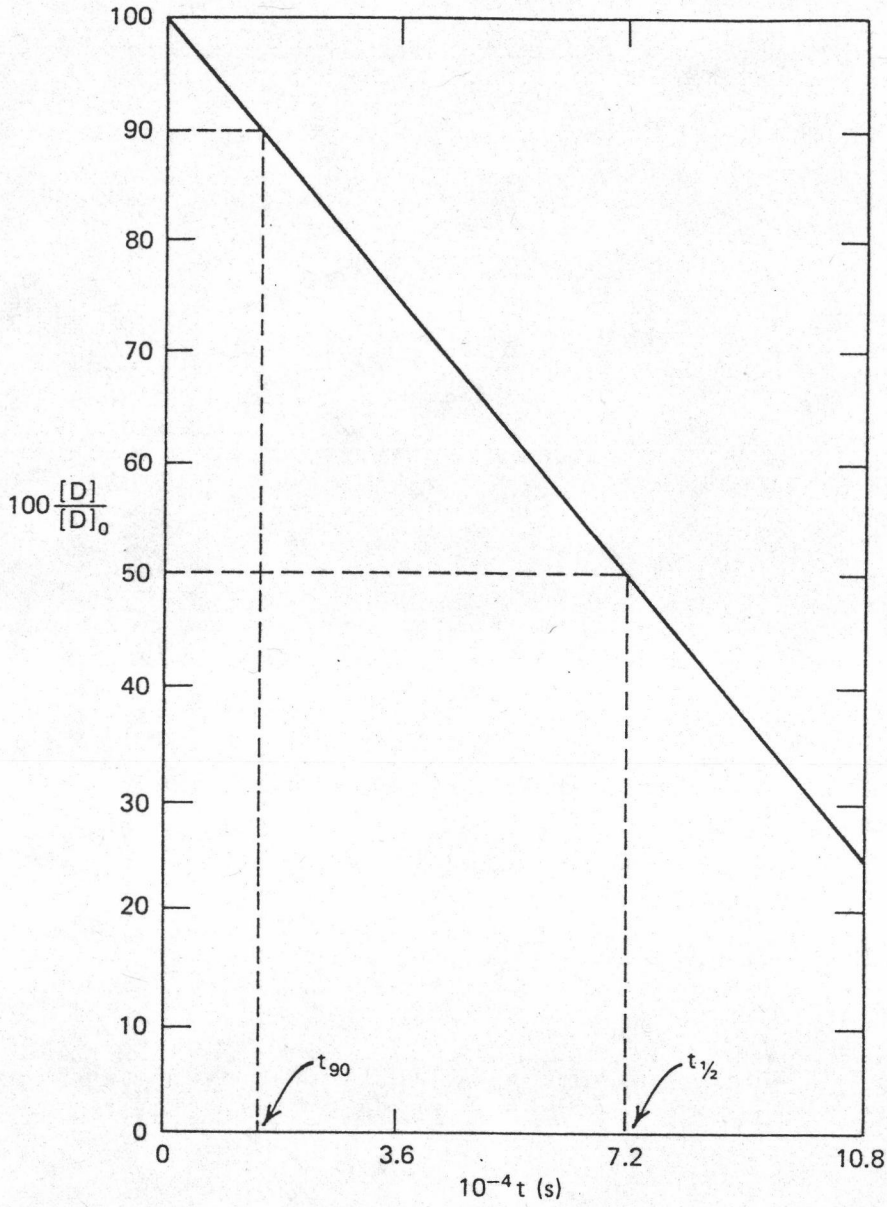


Figure 3. Percent of drug remaining as a function of time for a zero-order reaction.

2. Temperature Effects

2.1 Activation-Energy Calculations It was noted that 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 be expected that the reaction rate increases with increasing temperature. Experimentally, the reaction-rate constant is observed to have an exponential dependence on temperature:

$$k = Ae^{(-Ea/RT)} \qquad (14)$$

where k is the reaction rate constant of any order, A is the frequency factor, Ea is the Arrhenius activation energy of the chemical reaction, R is the gas constant, and T is the absolute temperature. This equation is the Arrhenius equation and can be written in several equivalent forms as follows:

$$\log k = \log A - Ea/2.303\,RT \qquad (15)$$

$$\log \frac{k_2}{k_1} = \frac{-Ea}{2.303\,R}\left(\frac{1}{T_1} - \frac{1}{T_2}\right) \qquad (16)$$

$$\log \frac{k_2}{k_1} = \frac{-Ea\,(T_2 - T_1)}{2.303\,RT_1T_2} \qquad (17)$$

where k_2 and k_1 are the rate constants at temperatures T_2 and T_1, respectively. The interpretation of Ea is as

follows: as the reaction proceeds from reactants to products the system must pass through a state of which energy is greater than that of the initial reactants (figure 4). This "barrier" is what prevents the reactants from immediately becoming the products; the activation energy is a measure of this barrier.

Equation (15) indicates that a graph of log k against 1/T will be linear with a slope of -Ea/R. This type of graph is called an Arrhenius plot (figure 5). From this plot A and Ea can be determined.

Stability of Indomethacin

Indomethacin decomposed by hydrolysis especially in the presence of hydroxide ions (Hajratwala and Dawson, 1977). Half lives of indomethacin in aqueous solutions at various pH values are shown in table 2 (Scott, 1980). The pathway of hydrolysis of indomethacin is shown figure 6. Figure 7 shows character of indomethacin degradation at various hydroxide ion concentrations. The indomethacin degradation follows first-order kinetics at all pH.

There have been attempted to studied how to stabilized indomethacin. One method was to micellize indomethacin in various surfactants as shown in table 3. These experiments were performed in alkaline condition to accelerate the degradation process.

Nonionic surfactants that had been used in most cases are series of polysorbates and pluronics. Polysorbate 80 decreased the rate constant of indomethacin

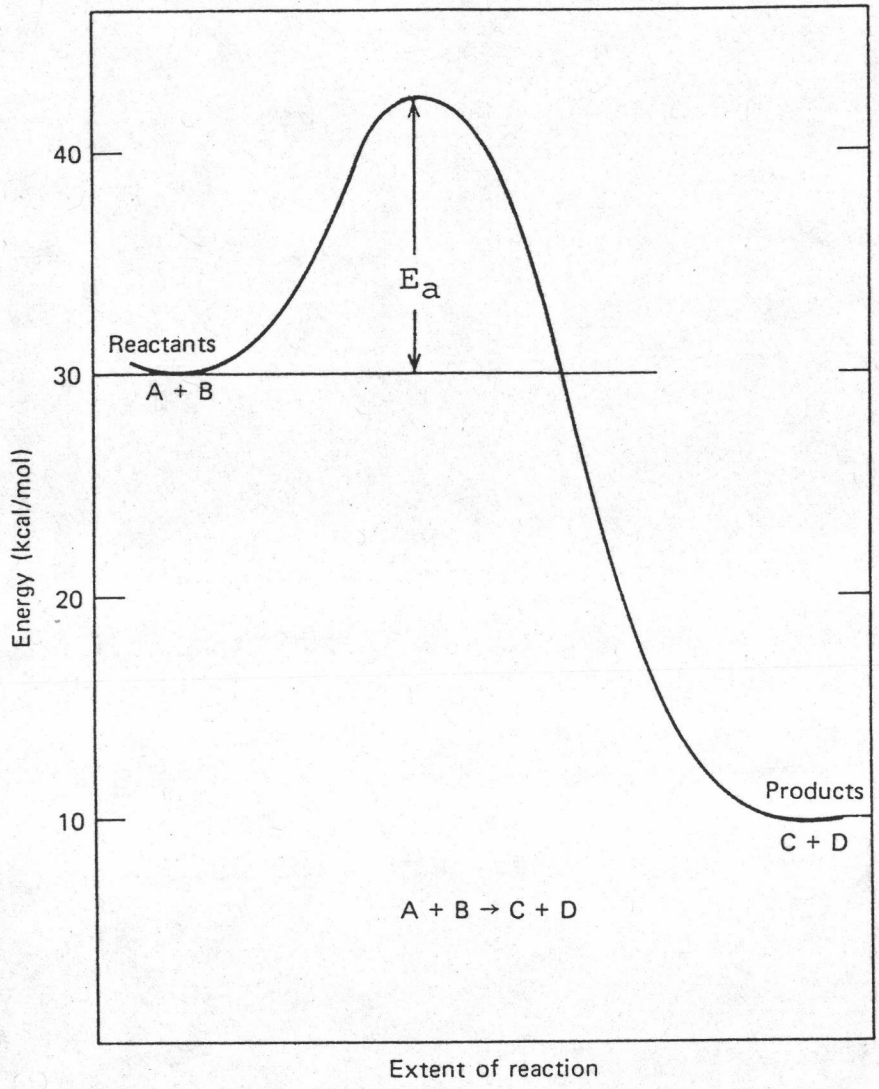


Figure 4. Schematic representation of how the energy of a system may change as a pair of reactant molecules A+B proceeds to products C+D.

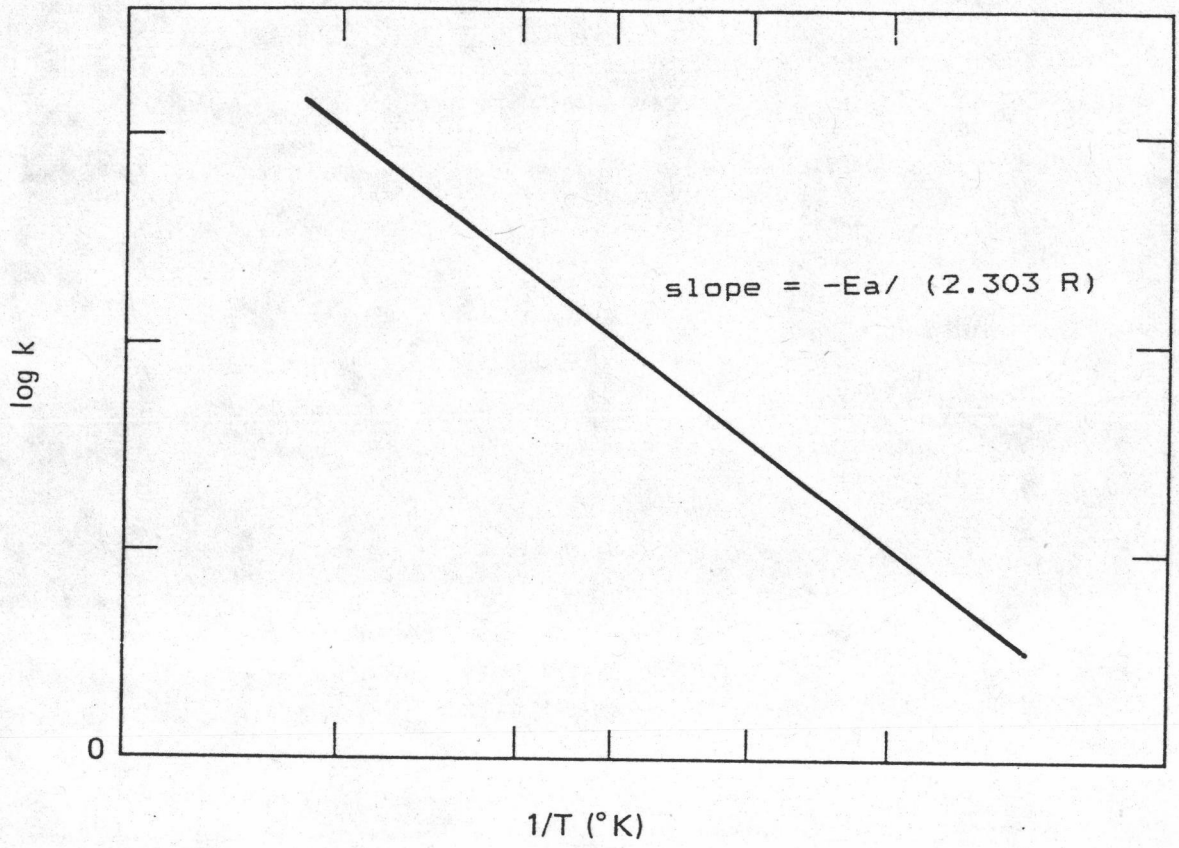
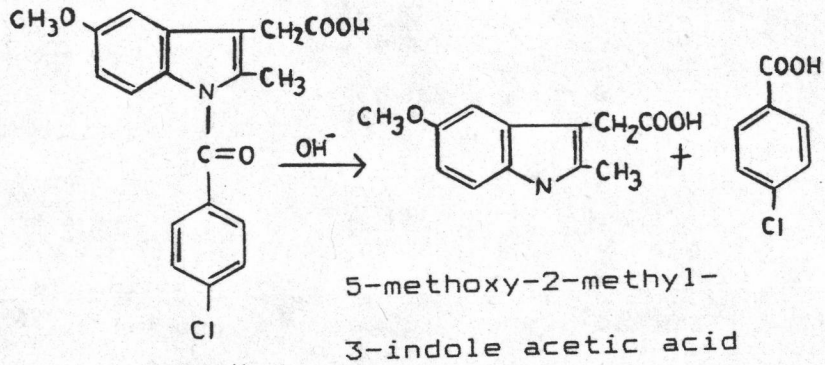


Figure 5. A typical Arrhenius plot of log k against 1/T.

Table 2 : The degradation rate of indomethacin in aqueous solutions at various pH values

pH	half-life
7.57	6.8 hours
8.14	3.1 hours
10.00	1-1.5 hours
12.00	1 minute



5-methoxy-2-methyl-
3-indole acetic acid

Indomethacin

p-chloro-
benzoic acid

Figure 6. Pathway of indomethacin hydrolysis.

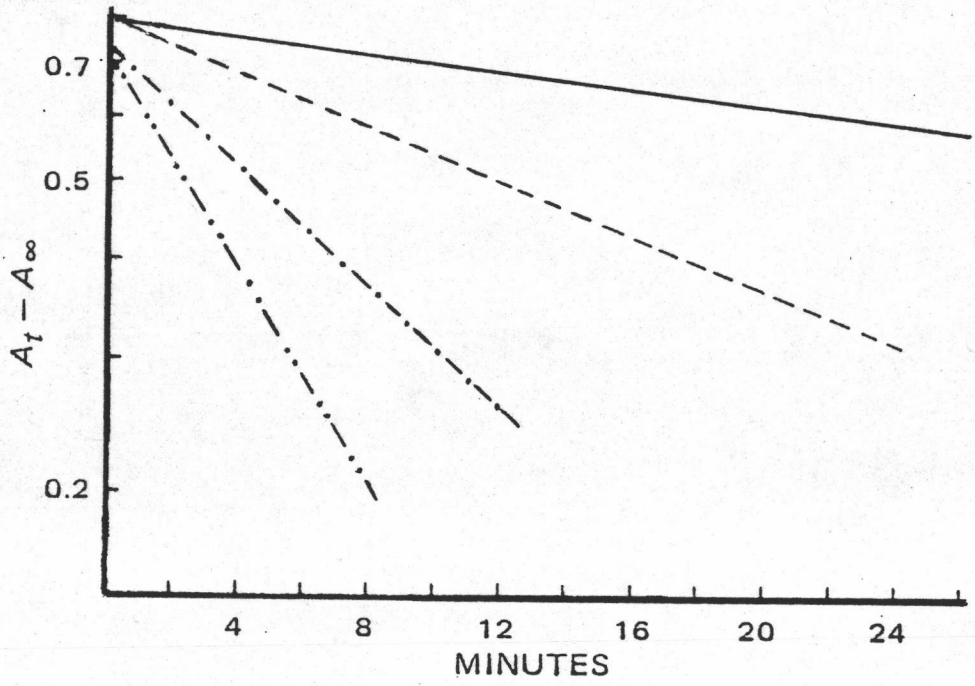


Figure 7. Plots showing overall first-order character of indomethacin degradation at various hydroxide-ion concentrations (M): 0.001, ———; 0.003, - - - ; 0.006, - • - ; 0.01, - • • - at 25.8 °C.

Table 3 : The effect of some surfactants on indomethacin stability

Type of surfactant	surfactant	change of rate constant
nonionic	ethoxylated lanolin	decrease [a]
	polysorbate 20, 40, 60	decrease [a,b]
	polysorbate 80	decrease [a,b,c]
	pluronic F68, F88, F108	decrease [d]
	pluronic F127	decrease [e]
cationic	cetrimonium bromide	increase [a]
	hexadecyltrimethyl ammonium bromide	increase [f]
anionic	sodium dodecyl sulfate	decrease [a]

[a] Dawson, Hajratwala and Taylor, 1977.
[b] Krasowska, 1979.
[c] Tsai, Yang and Naito, 1986.
[d] Lin and Kawashima, 1985.
[e] Tomida, Kuwada and Kiryu, 1988.
[f] Cipiciani, 1985.

decomposition the most among the various polysorbates (Krasowska, 1979; Tsai, Yang and Naito, 1986). Pluronics are newer nonionic surfactants. They interest formulators because of their extremely low order of toxicity and skin irritation, their reverse thermal gellation and their excellent compatibility with other ingredients. All pluronics that had been used in the studies decreased the rate of indomethacin hydrolysis (Lin and Kawashima, 1985; Tomida, Kuwada and Kiryu, 1988). The modifying effect of surfactants on the rate of degradation is usually explained on the basis of the two-phase model of solubilized systems and distribution of the drug between the aqueous and micellar phases. The postulation was made in this model that the rate is only in the bulk phase because the drug was firmly incorporated into the nonionic micelles and protected by it from the attacking species. The anionic surfactants protect the drug by pushing the attacking anions away. On the other hand, the cationic surfactants increase the rate of degradation by attracting hydroxide ions to react to the drug in micelles.