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EFFECT OF ZINC-ION ON INDOMETHACIN DEGRADATION IN ALKALINE AQUEOUS SOLUTIONS

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ABSTRACT

Kinetic studies have revealed that indomethacin degradation in the presence or absence of zinc-ion at different temperatures in alkaline aqueous solutions followed an apparent first-order rate constants. The rate constant-hydroxide-ion concentration profile was linear with a positive slope, suggesting the following rate law: $k_{obs}=k_1[OH^-]$. There was no significant difference in activation energy and other parameter values calculated for indomethacin degradation in the presence or absence of zinc-ion. Hence, zinc-ion was found to have no effect on its degradation.

INTRODUCTION

Indomethacin [1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid], a non-steroidal antiinflammatory agent, has been used in therapy in the form of various dosage forms. Its side effects, especially within the GI tract (disturbance, ulceration and bleeding), are always found by peroral administration (1). In order to avoid these adverse actions, zinc-indomethacin complex has been developed in our laboratory (unpublished data). Solubility and stability of drugs are always studied in order to maintain a suitable therapeutic formulation. However, this complex is practically insoluble in water unless it is alkaline , but degradation of indomethacin in alkaline media (pH 11-12) range at diffe-

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TABLE 1

Various Hydroxide-Ion Concentrations having a Constant Ionic-Strength (μ=0.5M)

$[OH^-]$,M	0.1M NaOH (ml)	0.1 NaCl (ml)	Water (ml)	Final Volume (ml)
0.005	0.5	4.95	4.55	10.0
0.015	1.5	4.85	3.65	10.0
0.025	2.5	4.75	2.75	10.0
0.040	4.0	4.60	1.40	10.0
0.050	5.0	4.50	0.50	10.0

rent temperatures has been reported (2). Hence, the aim of this study is to investigate the effect of zinc-ion on indomethacin degradation at different temperatures in alkaline aqueous solutions. Thermodynamic parameters obtained from Arrhenius plot for the degradation of indomethacin were also determined.

EXPERIMENTAL

Materials: Indomethacin[1] was used as received. All other chemicals were of analytical grade. All-glass triple-distilled water was used throughout.

Indomethacin Stock Solution: An accurately weighed quantity of indomethacin (9.8325 mg) was dissolved in 30 ml of ethanol (95% v/v), and the volume was adjusted to 100 ml with water at room temperature.

Sodium Hydroxide Solution: To sodium hydroxide solution (0.1M), sodium chloride solution (1M) was added to adjust the ionic strength, μ, of the solution was calculated by the equation (I).

$$\mu = \tfrac{1}{2}\,\Sigma[i].Z_i^2 \qquad \text{(Eqn.I)}$$

Where, [i] and Z_i are concentrations and the net charge of the ion i, and Σ implies a summation over all the ions in the solution.

[1]Supplied by Ranbaxy Laboratories Ltd., New Delhi (India)

The different hydroxide-ion concentrations having a constant ionic strength (μ=0.5M) is given in Table 1.

Zinc Acetate Stock Solution: A stock solution of zinc acetate ($2x10^{-4}$ M) was prepared by dissolving zinc acetate (4.39 mg) in water (100 ml).

Kinetic Studies : To 2 ml of indomethacin stock solution, 1 ml each of 0.005, 0.015, 0.025, 0.040 and 0.05 M hydroxide-ion concentration solution (Table 1) was added and the final volume was made upto 5 ml with water to give final hydroxide-ion concentrations of 0.001, 0.003, 0.005, 0.008 and 0.01M, respectively. These mixtures were immediately transferred to a quartz cell kept in a constant temperature cell holder[2]. The initial concentration of indomethacin in the reaction cell was approximately $1.1x10^{-4}$M.

Absorbance (against an appropriate blank) was recorded as a function of time at λ_{max} 318 nm. The absorbance data obtained were used to construct semilogarithmic plots of the function per cent (A_t-A_∞) versus time, where A_t is the observed absorbance at time, t (min) and A_∞ is the observed equilibrium absorbance values. The plots are illustrated in Fig.1, where the degradation behaviour is observed to follow first-order kinetics. The apparent first-order rate constants, K_{obs} (Table 2) were calculated using regression analysis. Correlation coefficients were between -0.997 and -0.999.

Effect of Hydroxide-Ion Concentration and Temperature: The study was carried out in various concentrations of hydroxide-ion at 25, 37 and 45°C.

Effect of Zinc-Ion on Indomethacin Degradation: To study the effect of zinc-ion on indomethacin degradation the above procedure was carried out with the exception that the final volume to 5 ml was adjusted with zinc acetate solution ($2x10^{-4}$ M) instead of water.

[2] UV/Vis Spectrophotometer (Hitachi, Model 330) with a temperature controller SPR-7 and a thermostated section for cell H-300.

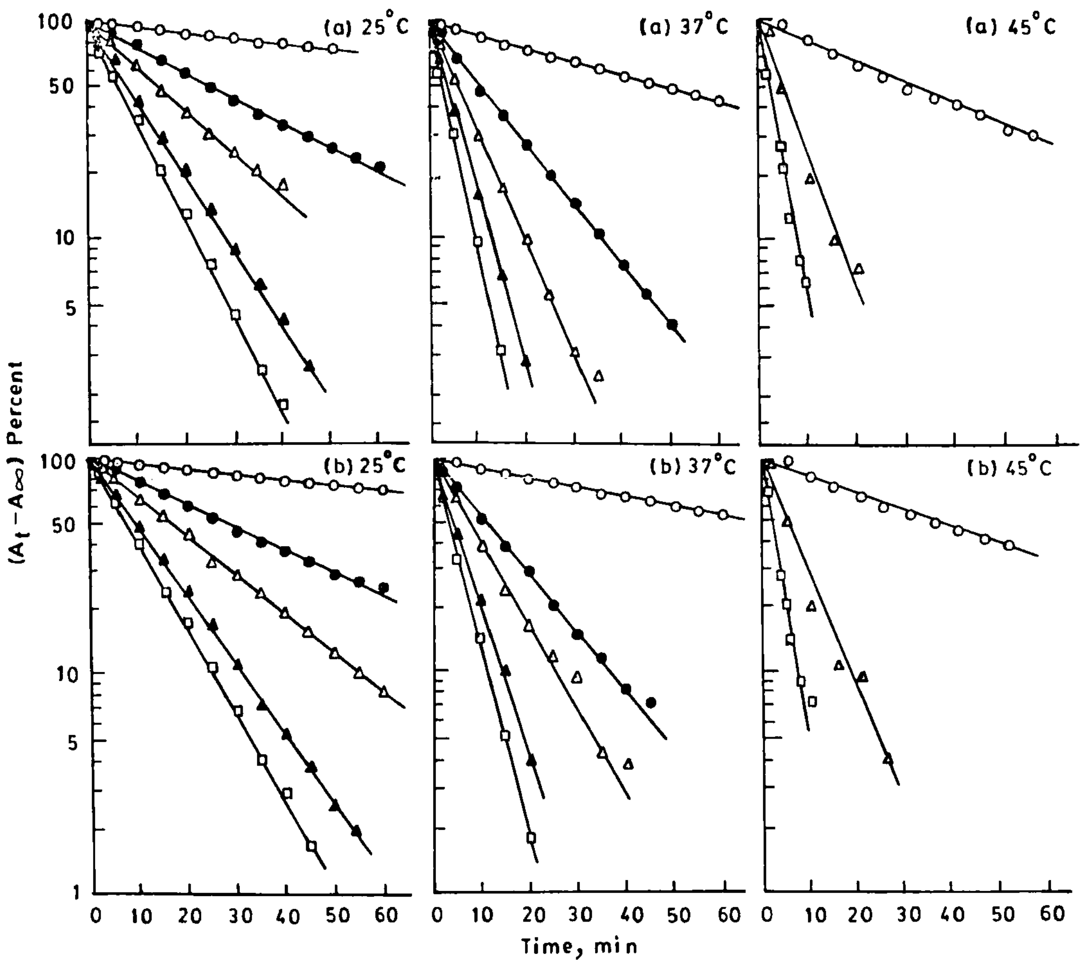

FIGURE 1

Influence of temperature on the degradation of indomethacin in (a) absence, or (b) presence of zinc-ion at varying hydroxide-ion concentrations; O, 0.001; ●, 0.003; Δ , 0.005; ▲ , 0.008; and □ , 0.01M.

TABLE 2

Effect of Hydroxide-Ion Concentration on the Apparent First-Order Rate Constant, k_{obs} for Indomethacin Degradation in (a) Presence or (b) Absence of Zinc-Ion at Various Temperatures.

$[OH^-]$,M	$k_{obs} \times 10^2$, min^{-1}					
	25°		37°		45°	
	a	b	a	b	a	b
0.001	0.57	0.56	0.99	1.30	1.87	2.14
0.003	2.40	2.62	6.10	6.32	-	-
0.005	4.16	4.58	8.80	11.34	12.74	14.20
0.008	7.28	8.06	15.52	17.65	-	-
0.010	8.99	10.35	19.65	22.89	28.39	30.35

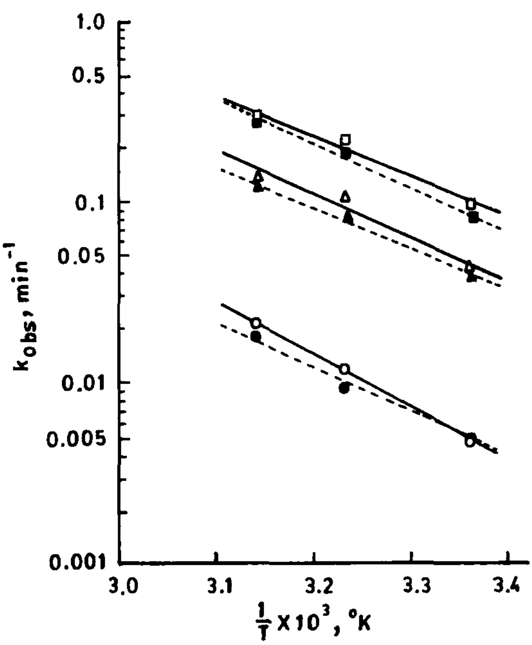

FIGURE 2

Influence of varying concentrations of hydroxide-ion on indomethacin degradation in (a) absence, or (b) presence of zinc ion at various temperatures; (a):O, 25; Δ, 37°; □ 45°; (b): ●, 25°, ▲, 37° and ■, 45°C

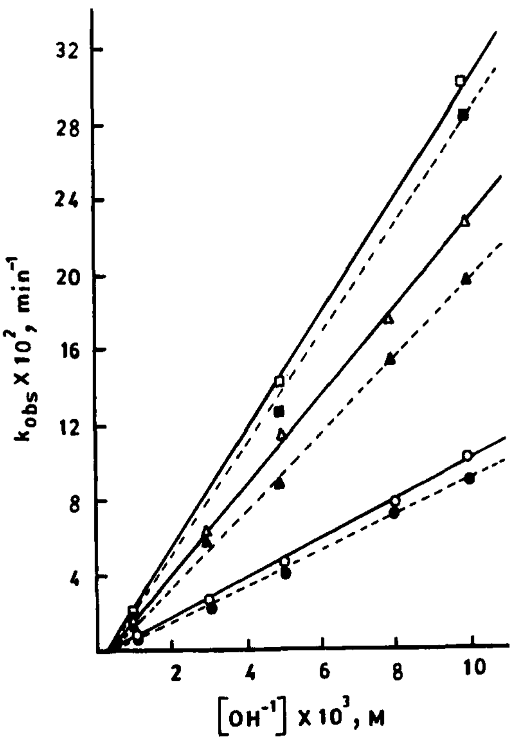

FIGURE 3

Arrhenius plots showing temperature dependence of K_{obs}, the apparent first-order indomethacin degradation constant in (a) absence, or presence of zinc-ion at various hydroxide-ion concentrations (M); (a) —— , O, 0.001M; Δ , 0.005M and □ , 0.01M; (b) - - - , ●, 0.001M; ▲ , 0.005M, and ■ , 0.01M

RESULTS AND DISCUSSION

The absorption data showed that the degradation of indomethacin in 0.01M hydroxide-ion concentration with or without zinc-ion reached maximum after 45 min at 25°, in 15 min at 37° and within 10 min at 45°C. Since this degradation reaction is catalytic (2), it was assumed that the equilibrium absorbance for other hydroxide-ion concentrations would be same as that of the former. Figure 1 indicates that the indomethacin degradation in the presence of

TABLE 3

Thermodynamic Parameters for the Alkaline Hydrolysis of Indomethacin in (a) Presence, or (b) Absence of Zinc-Ion at 37°C obtained from Arrhenius-type Plots

$[OH^-]$,M	E_a, Kcal/mole		ΔH*, Kcal/mole		ΔS*,e.u.,		ΔG*, Kcal/mole	
	a	b	a	b	a	b	a	b
0.001	10.57	12.36	9.95	11.75	-35.69	-31.04	21.02	21.37
0.005	10.19	10.48	9.58	9.86	-32.58	-31.14	19.68	19.51
0.010	10.55	9.87	9.93	9.26	-29.81	-31.69	19.18	19.08

zinc-ion at varying hydroxide-ion concentrations at temperatures 25, 37 and 45° was similar to that of observed data without zinc-ion.

The plots of rate constants (k_{obs}) versus hydroxide-ion concentrations (Fig.2) in the presence or absence of zinc-ion at different temperatures have similar slope values when calculated using regression analysis.Correlation coefficient values (0.997-0.999) were fairly good. The rate constant-hydroxide-ion concentration profile suggests a simple mechanism as proposed by Hazratwala and Dawson (2). The reaction mechanism shown in Scheme 1, employed to study indomethacin degradation kinetics (2), would give a rate constant-hydroxide-ion concentration profile that fits the experimental points well.

$$I^- + OH^- \xrightarrow[\text{Scheme 1}]{k_1} \text{Products}$$

where I^- is the monodissociated indomethacin species, and, $k_{obs} = k[OH^-]$,i.e. the rate constant is dependent upon hydroxide-ion concentration.

The effect of temperature on the reaction rate can be expressed using the Arrhenius-equation. As shown in Fig.3, plots of log k_{obs} versus 1/T yield a straight-line relationship at all hydroxide-ion concentration used. The activation energy values (3) and other thermodynamic parameters according to the transition state theory (3) calculated are given in Table 3. These values are in good agreement with the earlier report (2). There is no significant difference in these values calculated for indomethacin degradation in the presence or absence of zinc-ion. Hence, it can be concluded that zinc-ion does not modify indomethacin degradation kinetics at the various hydroxoide-ion concentrations studied. The present investigation is augmented by report of Jean et al.(4). They showed that alkaline earth metals and heavy metals had no effect on indomethacin degradation.

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