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Kinetics of decomposition of irbesartan in aqueous solutions determined by high performance liquid chromatography

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The kinetics of breakdown of irbesartan in aqueous solutions at elevated temperatures has been investigated by a high performance liquid chromatography method. The reaction is found to follow first-order kinetics and the rate constant for the degradation at 25 °C is estimated by extrapolation. The decomposition of irbesartan is shown to be hydroxide ion catalysed and the effects of ionic strength and buffer concentrations to such rate studies are discussed.

1. Introduction

Irbesartan, 2-n-butyl-4-spirocyclopentane-1- [(2′-tetrazol-5-yl)biphenyl-4-yl) methyl]-2-imidazolin-5-one, is a potent, long-acting, non-peptide AII receptor antagonist with high specificity for the AT1 subtype (Waber 2001; Gillis 1997). Clinically irbesartan is administered in tablets for the treatment of hypertension. Based on its mechanism of action, irbesartan has the potential to offer advantages in safety and tolerability over previous classes of drugs in the treatment of hypertension, diabetic nephropathy and heart failure (Cazaubon et al. 1993).

As the efficacy of a pharmaceutical preparation depends on the stability of the active substance in the dosage form, this investigation was undertaken to determine irbesartan stability under various aqueous conditions and temperatures.

Prior to this study, no chromatographic investigation of irbesartan and its degradation products has been reported, and in this paper, we report on the use of HPLC for the determination of rate constants of irbesartan in aqueous buffer solutions.

2. Investigations, results and discussion

The calibration graph of irbesartan obeyed Beer's law over concentration range of 10.0–50.0 ppm. Peak area ratio versus concentration relationship is described by regression equation:

$$A = 0.0700 + 0.1063\,C \quad (R^2 = 0.9999) \qquad (1)$$

The kinetics of hydrolysis of irbesartan was studied in aqueous solution at various temperatures over the pH range 2.00–9.80. At the pH range 2.00–5.00, no degradation of irbesartan was observed, but at the pH values, where decomposition occured, irbesartan and the mixture of degradation products were successively resolved. A typical chromatogram obtained from the hydrolysis is shown in Fig. 1. Irbesartan and its degradation product were separated in a single chromatogram in less than 5 min.

At constant pH and temperature, the reaction was found to be represented as first-order with respect to irbesartan in all solutions. The degradation was followed till less than 5% of irbesartan peak height remained. The influence of pH on

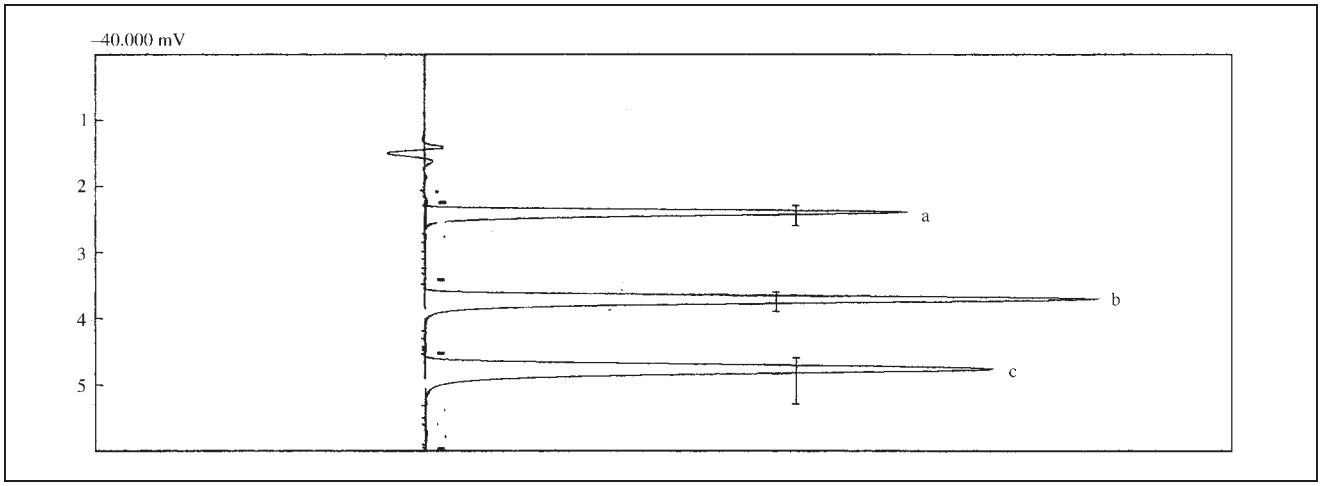

Fig. 1: Chromatogram of irbesartan, benzoic acid (internal standard) and degraded product. Peak a = internal standard Peak b = degraded product Peak c = irbesartan

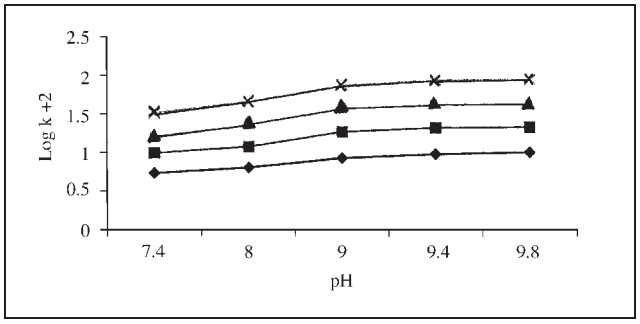

Fig. 2: Plot of logarithm of rate constant (k) against pH. ■——■ 37 °C ■——■ 50 °C ▲——▲ 60 °C X——X 70 °C

the degradation rate for irbesartan is shown in Fig. 2, where the logarithm of the observed apparent first-order rate constant is plotted against pH. The graph obtained indicated a hydroxide ion catalysed decomposition. The mechanism of reaction may be represented as A → P where A and P are the concentrations of irbesartan and the degraded product respectively. The corresponding rate equation is:

$$-dA/dt = kA, A \rightarrow P \qquad (2)$$

where k is the apparent rate constant for the decomposition.

Table 1 summarizes the kinetics results obtained. The results indicate that at constant pH, the rate constant was observed to increase with increase in temperature. The increase was found to be about a 2- fold increase per 10 °C rise in temperature. The effects of buffer concentration and ionic strength were studied at pH 9.80 and pH 7.40 respectively and the results are reported in Table 2. The results show the rate constant to be unaffected by buffer concentrations indicating lack of general base catalysis. It was also observed that the rate constant was independent of the ionic strength of the buffer composition. Such lack of dependence of the rate constant on ionic strength was futher confirmed when a plot of logarithm of the observed rate

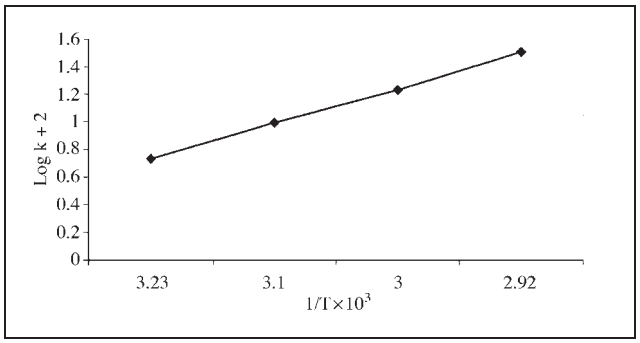

Fig. 3: Plot of logarithm of rate constant (k) against temperature at pH 7.40

Table 2. Effect of buffer concentration and ionic strength on first-order rate constants (k), 37 °C

Buffer concentration (pH 9.80)		Ionic strength (pH 7.40)	
Concentration (mol/l)	k (mean ± % SD/h)	Kcl (mol/l)	k (mean ± % SD/h)
0.025	0.1002 ± 0.027	0.050	0.0544 ± 0.026
0.050	0.1012 ± 0.051	0.100	0.0562 ± 0.033
0.075	0.0997 ± 0.032	0.150	0.0539 ± 0.019
0.100	0.1008 ± 0.048	0.200	0.0578 ± 0.046
0.125	0.0984 ± 0.022	0.250	0.0556 ± 0.042
0.150	0.1019 ± 0.038	0.300	0.0569 ± 0.053
		0.350	0.0549 ± 0.031
		0.400	0.0542 ± 0.023

constant versus the ionic strength gave a zero slope. The influence of temperature on the degradation rate for irbesartan at physiological pH 7.4 is shown in Fig. 3, where the logarithm of the observed apparent first-order rate constant is plotted against the reciprocal of the absolute temperature. The measured values for rate constants conformed to the Arrhenius equation over the range of temperature used ($R^2 = 0.9953$). This indicated a single mechanism which justified the extrapolation of the results to obtain a rate constant of 0.0246/h at 25 °C. Using the Arrhenius equation the activation energy for the primary decomposition of irbesartan is estimated to be 47.7 kJ/mol. Estimated activation energies at pH values 8.00, 9.00, 9.40 and 9.80 and 25 °C were found to increase with increase in pH until pH 9.8 where a levelling effect was observed. The half-lives of decomposition at various pH values and 25 °C were found to be 28 h, (pH 7.40), 26 h (pH 8.00), 21 h (pH 9.00), 19 h (pH 9.40) and 17 h (pH 9.80).

The IR spectra of irbesartan and the degraded product gave the following vibrational frequencies: Irbesartan: 2980 (C−H, triplets, Ar), 1730 (C=O), 1620 (C=N), 1550 (C=C, Ar), 1430 (N=N) and 1400 (α-CH_2). Degraded product: 2990 (C−H, triplets, Ar), 1640 (C=N), 1580 (C=C, Ar) and 1445 (N=N). The carbonyl functional group of the lactam ring and the α-methylene group, both present in irbesartan were found to be absent in the degraded product.

On the basis of the IR spectra of irbesartan and the degraded product, a plausible reaction mechanism of the hydrolysis is the cleavage of the n-butyl-spirocyclopentane-imidazolinone side chain to give methyl-biphenyltetrazole as the degraded product. The results obtained from correlation coefficients and standard deviations of the rate constants indicate that the chromatographic method used in this study is adequately precise. The degradation was found to follow first-order kinetics and the reaction was hydroxide ion catalysed decomposition. Buffer concentration or ionic strength of buffer composition had no effect on the rate constant. The half-life (13 h) obtained at phy-

Table 1: First-order rate constants (k) of irbesartan decomposition in aqueous solutions at elevated temperatures (μ = 0.4 mol/l)

pH	Buffer	k (mean ± % SD/h)			
		Temperature (°C)			
		37	50	60	70
2.01	Hydrochloric acid	–	–	–	–
5.03	Acetate	–	–	–	–
7.40	Phosphate	0.0540 ± 0.020	0.0986 ± 0.060	0.1708 ± 0.055	0.3246 ± 0.027
8.02	Borate	0.0638 ± 0.025	0.1193 ± 0.030	0.2397 ± 0.024	0.4581 ± 0.049
9.01	Borate	0.0850 ± 0.050	0.1864 ± 0.032	0.3918 ± 0.035	0.7444 ± 0.036
9.43	Borate	0.0955 ± 0.036	0.2108 ± 0.035	0.4309 ± 0.038	0.8717 ± 0.047
9.81	Borate	0.1010 ± 0.056	0.2154 ± 0.046	0.4456 ± 0.055	0.8972 ± 0.060

siological pH 7.4 and a temperature of 37 °C supports the prescription regimen of irbesartan in clinical treatment of hypertension.

3. Experimental

3.1. Materials and apparatus

Irbesartan was obtained from Bristol-Meyers Squibb (USA) and benzoic acid (internal standard) was purchased from Fisher Scientific (USA). All the other organic solvents used were of HPLC grade (Fisher Scientific, USA). All separations were carried out with Hitachi LC 6200 pump and LC Organizer injector, Kratos Spectroflow 783 detector. A zorbax analytical column C18, 150 mm × 4.6 mm, 3.5 μm was used.

3.2. Chromatographic procedure

The mobile phase consisted of 1% aqueous acetic acid in methanol. The flow rate was 1 ml/min. at room temperature. The injection volume was 10 μl and detection was effected at 254 nm.

3.3. Standard solutions

Stock solutions of irbesartan (100.0 ppm) and internal standard (400.0 ppm) were prepared in methanol. Aliquots (10.0–50.0 ppm) of the standard stock solution were pipetted into a 10 ml volumetric flask. A 1-ml aliquot of the internal standard solution was added to each flask and diluted to volume with methanol.

3.4. Kinetic measurement

The rate studies were performed in aqueous buffer solutions at 37.0, 50.0, 60.0 and 70.0 ± 0.1 °C. Hydrochloric acid, acetate, phosphate and borate were used as buffers. The total buffer concentration was 0.1 mol/l and a constant ionic strength (μ) of 0.4 was maintained for each buffer by adding a calculated amount of potassium chloride. Stock solution of irbesartan in methanol was added to the buffer solution to give a concentration of 50.0 ppm. The solutions were kept in a water-bath at various temperatures and at appropriate intervals, aliquots were withdrawn and injected into the chromatograph after the addition of internal standard. The rate constants were determined from the slopes of linear plots of $\log C_t$ versus time, where C_t are the concentrations of irbesartan at time t, calculated from the calibration graph of irbesartan. The calibration graph was constructed by ploting the peak area ratio of irbesartan to internal standard against the standard concentration of irbesartan.

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