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

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

1. Introduction

Rabeprazole sodium, {[(4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl)-sulfinyl}-1 *H*-benzimidazole sodium salt is a substituted benzimidazole proton pump inhibitor (Prakash and Faulds 1998; Robinson 2004). Clinically, rabeprazole sodium is administered as delayed-release enteric coated tablets for the treatment of gastroesophageal reflux disease, duodenal ulcers and pathological hypersecretory conditions, including Zollinger-Ellison syndrome. Rabeprazole acts by blocking irreversibly the hydrogen-potassium adenosine triphosphatase enzyme system (the K^+/H^+-ATPase – the proton pump) of the gastric parietal cell and has been shown to be a more rapid inhibitor of proton pump than omeprazole, lansoprazole or pantaprazole (Williams and Pounder 1999; Ohning et al. 2003). As the efficacy of a pharmaceutical preparation requires the stability of the active substance in the dosage form, this investigation was undertaken to determine rabeprazole sodium stability in aqueous solution under various conditions and temperatures. Various analytical methods have been employed in stability studies, however high performance liquid chromatography has the advantage of much higher specificity than spectrophotometric method and can provide qualitative and quantitative information on the degradation products (Taylor and Sood 1978). Although El-Gindy et al. (2003) have investigated the kinetics of the oxidative and photo degradation processes of rabeprazole in Britton-Robinson buffer solutons by HPLC method, this work was carried out to investigate the hydrolysis of rabeprazole sodium in aqueous solutions (buffered and unbuffered) at elevated temperatures.

2. Investigations, results and discussion

The calibration graph of rabeprazole sodium was linear in the concentration range of 20.0–100.0 µg/mL. A plot of peak area ratio against concentration is described by the regression equation

$$A = 0.0062 + 0.0481\,C\ (R^2 = 0.9994)\,.$$

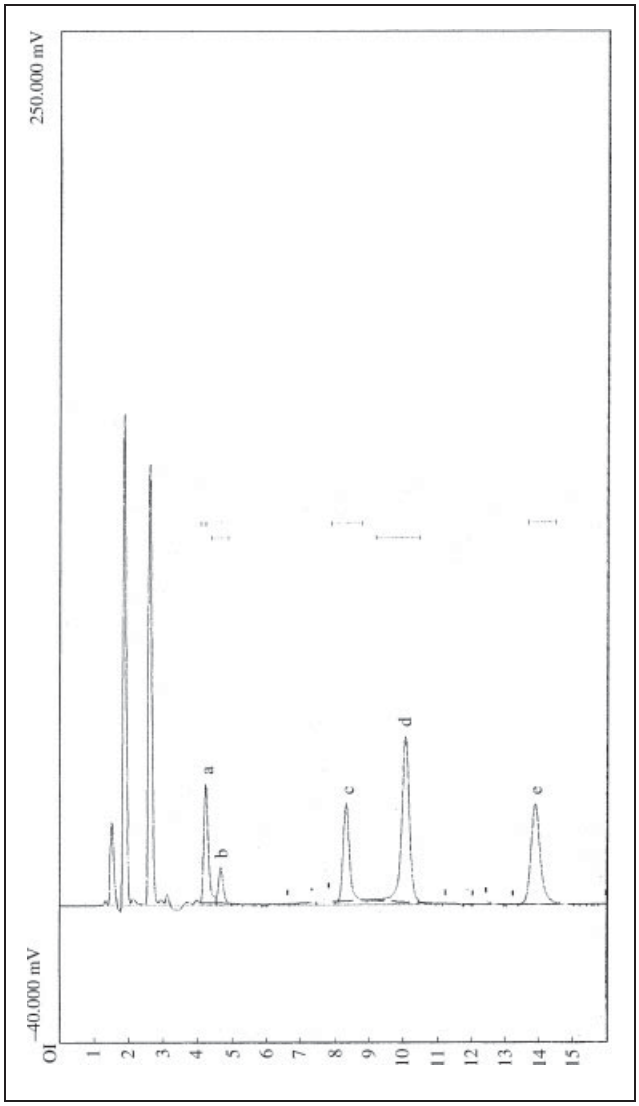

Fig. 1: Chromatogram of rabeprazole sodium, benzaldehyde (internal standard) and degraded products: a – c degraded products; d = internal standard; e = rabeprazole sodium

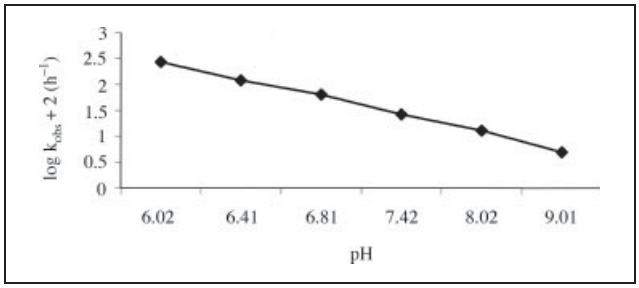

Fig. 2: Plot of logarithm of rate constant against pH

The kinetics of hydrolysis of rabeprazole sodium was studied in distilled water at 40, 50, 60 and 70 °C. With buffer solutions, the pH range studied was 3.0–9.0 at 37 °C. At the pH range of 3.0–5.0, rabeprazole sodium was so unstable that it was difficult to follow the reaction rate, but at pH values 6.0–9.0 where the reaction rate was monitored rabeprazole sodium and the mixture of degradation products peaks were completely resolved. A typical chromatogram obtained from the hydrolysis is shown in Fig. 1. Rabeprazole sodium and its degraded products were separated in a single chromatogram in less than 15 min. At constant pH and temperature, the reaction was found to be represented as first-order with respect to rabeprazole sodium in all solutions. The degradation was followed until less than 10% of rabeprazole sodium peak height remained. The influence of pH on the degradation rate for rabeprazole sodium is shown in Fig. 2, where the logarithm of the observed apparent first-order rate constant is plotted against pH. The graph obtained indicated water and hydrogen ion catalysed decomposition. Thus the rate equation can be described as

$$k_{obs} = k_o + k_H^+ [H^+]$$

where k_o is the apparent catalytic rate constant in water, k_H^+ is the apparent hydrogen ion catalytic rate constant, $[H^+]$ is the hydrogen ion concentration and k_{obs} is the observed apparent first-order rate constant. The apparent first-order rate constant for the water-catalysed and the second-order rate constant for hydrogen ion catalysed degradation were determined to be 0.2111/h and 2.6×10^6/mol/h respectively. In water, 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. Table 1 summarizes the kinetics results obtained. The pH of water was observed to remain unaltered throughout the stability study. The effects of

Table 1: First-order rate constant of rabeprazole sodium decomposition in aqueous solutions

pH	Medium	Temperature (°C)	k_{obs}[b] (h^{-1})
3.07	Hydrochloric acid	37[a]	–
5.03	Acetate buffer	37[a]	–
6.02	Phosphate buffer	37[a]	2.715 ± 0.338
6.41	Phosphate buffer	37[a]	1.202 ± 0.263
6.81	Phosphate buffer	37[a]	0.635 ± 0.828
7.40	Phosphate buffer	37[a]	0.266 ± 2.447
8.01	Borate buffer	37[a]	0.128 ± 6.508
9.02	Borate buffer	37[a]	0.049 ± 1.388
Water		40	0.244 ± 2.016
Water		50	0.596 ± 0.544
Water		60	1.278 ± 0.550
Water		70	2.500 ± 0.222

[a] μ = 0.4 mol/L
[b] Mean ± RSD (%), n = 3

Table 2: Effect of buffer concentration and ionic strength on first-order rate constant

Buffer concentration		Ionic strength	
(mol/L)[a]	k_{obs} [c](h^{-1})	KCl (mol/L)[b]	k_{obs} [c](h^{-1})
0.025	2.695 ± 0.256	0.100	0.266 ± 2.162
0.050	2.724 ± 0.149	0.150	0.271 ± 2.531
0.075	2.679 ± 0.222	0.200	0.260 ± 3.508
0.100	2.687 ± 0.239	0.250	0.268 ± 2.231
0.125	2.762 ± 0.092	0.300	0.263 ± 3.122
0.150	2.680 ± 0.293	0.400	0.264 ± 2.481

[a] 37 ± 1 °C, pH 6.02; NaOH–KH_2PO_4, [b] 37 ± 1 °C, pH 7.40; NaOH–KH_2PO_4
[c] Mean ± RSD (%), n = 3
Same ionic strength (0.4 mol/L) was maintained in both buffers with KCL

buffer concentration and ionic strength were studied at pH 6.02 and 7.40, respectively and the results are reported in the Table 2. The results indicate that rate constant is unaffected by buffer concentrations indicating lack of general acid catalysis. It was also observed that the rate constant was independent of the ionic strength of the buffer solutions. Such independence of the rate constant on ionic strength was further confirmed when a plot of logarithm of the observed rate constant against the ionic strength produced a zero slope. The influence of temperature on the degradation rate for rabeprazole sodium in water 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 the rate constants conform to the Arrhenius equation over the range of temperatures studied ($R^2 = 0.9993$). This showed a single mechanism which justified the extrapolation of the results to obtain a rate constant of 0.0654/h at 25 °C. Using the Arrhenius equation the activation energy and the frequency factor for the primary decomposition of rabeprazole sodium is estimated to be 69.1 kJ/mol and 8.5×10^{10}/h respectively. A high value of the frequency factor indicates a large proportion of collisions between rabeprazole sodium molecules and hydrogen ions during the degradation reactions. It also suggests an entropy increase during the reactions (Sykes 1986). The half-life of decomposition at 25 °C was found to be 10.6 h. In this investigation, no attempt was made to assign structures to the degraded products nor indicate if they are the final products or intermediates. A plausible reaction mechanism of the hydrolysis is the cleavage of methyl-sulfinyl bond to give 2,3-dimethyl-4-methoxypropoxy pyridine and sulfonyl derivative of benzimidazole, followed by subsequent cleavage of the 4-methoxypropoxy group to give 2,3-dimethyl-4-hydroxyl pyridine.

The breakdown of rabeprazole sodium was found to follow first-order kinetics and the reaction was water and hydrogen ion catalysed degradation. Ionic strength of buffer solution or buffer concentration had no effect on the

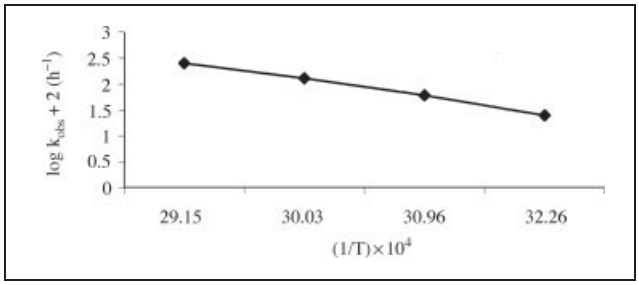

Fig. 3: Plot of logarithm of rate constant against temperature

rate constant. The half-lifes (2.6 h) obtained at physiological pH 7.4 and 37 °C support the prescription regimen of rabeprazole sodium used in the clinical treatment of ulcerative conditions. Reported plasma half-life is 1–2 h and recommended adult oral dose is one 20 mg delayed-release tablet to be taken once daily for four to eight weeks (Lasaw 2005). Finally, as the degradation of rabeprazole sodium is so rapid under acidic conditious, future study would reqiure the incorporation of additives into buffer solutions with the objective of reducing the reaction rate.

3. Experimental

3.1. Materials

Rabeprazole sodium (Eisai Co., Japan), benzaldehyde (Aldrich-Sigma Co., USA) and all the organic solvents used were of HPLC grade (Fisher Scientific, USA).

3.2. Apparatus

All separations were carried out with Hitachi LC 6200 pump and LC Organizer injector (Hitachi Co., Japan), Kratos Spectroflow 783 detector (Spectral Physics, USA) and Zorbax analytical column C_{18}, 150 × 4.6 mm, 3.5 μm (Agilent Technologies, USA).

3.3. Chromatographic procedure

The mobile phase consisted of phosphate buffer-acetonitrile (75 : 25, V/V). The flow rate was 1 ml/min at room temperature. The injection volume was 10 μl and detection was effected at 254 nm.

3.4. Buffer solutions

The following buffers were used for the stability investigations: KCl−HCl, pH 2–3 ; $CH_3COOH-CH_3COONa$ trihydrate, pH 5; $NaOH-KH_2PO_4$, pH 6–7.4; $H_3BO_3-NaOH-KCl$, pH 8–9. Conatant ionic strength (μ) of 0.4 mol/L was maintained for each buffer by adding calculated amount of KCl.

3.5. Standard solutions

Stock solutions of rabeprazole sodium (1000 μg/ml) and internal standard (benzaldehyde, 40 μg/ml) were prepared in methanol. Aliquots of the standard stock solution were pipetted into a 10 ml volumetric flask. A 1-ml aliquot of internal standard solution was added to each flask and diluted to volume with methanol to give final concentration of 20–100 μg/ml rabeprazole sodium.

3.6. Kinetic measurement

The rate studies were performed in distilled water at 40.0, 50.0, 60.0 and 70.0 ± 1 °C and buffered aqueous solutions at 37 ± 1 °C. The total buffer concentration was 0.1 mol/L and a constant ionic strength of 0.4 mol/L was maintained for each buffer by adding a calculated amount of potassium chloride. Stock solution of rabeprazole sodium in water was diluted with water (unbuffered) or added to the buffer solution (buffered) to give a concentration of 100 μg/ml. The solutions were kept in an oven 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 is the concentration of rabeprazole sodium at time t calculated from the calibration graph of rabeprazole sodium. The calibration graph was constructed by ploting the peak area ratio of rabeprazole sodium to internal standard against the standard concentration of rabeprazole sodium.

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