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Olanzapine degradation kinetics in aqueous solution

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Received June 23, 2010, accepted June 28, 2010

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Pharmazie 66: 168–170 (2011) *doi: 10.1691/ph.2011.0185*

The degradation kinetics of olanzapine as a function of pH and temperature has been studied by a spectrophotometric method. The degradation reaction rates were observed to follow first-order kinetics with respect to olanzapine. The hydrolytic reaction was shown to be hydrogen and hydroxide ion-catalyzed and the Arrhenius plots showed the temperature dependence of olanzapine degradation.

1. Introduction

Olanzapine, 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno [2,3-*b*][1,5]benzodiazepine is a second generation antipsychotic agent (so-called atypical antipsychotics) and belongs to the class of thienobenzodiazepine (Manickan et al. 1997; Reggi et al. 2000; Bao and Potts 2001). Clinically, olanzapine is used in the management of schizophrenia and for the treatment of moderate to severe mania associated with bipolar disorder. It acts by antagonizing serotonin (5-HT_2), muscarinic, histamine (H_1) and adrenergic (α_1) receptors as well as dopamine (D_1/D_2) receptors (Sweetman 2006; Katzung 2007). This investigation was undertaken to study olanzapine stability under various aqueous conditions and temperatures because potency and efficacy of any pharmaceutical preparation depends on the stability of its active ingredient. A previous study (Shah et al. 2008) reported that olanzapine could degrade under acidic and basic conditions, however, little or no information exists regarding its degradation kinetics in aqueous solution. The purpose of this study was to investigate the effects of acid-base catalysis, temperatures on the stability of olanzapine using spectrophotometric assay method.

2. Investigations, results and discussion

The correlation coefficient of the detector linearity for olanzapine in the concentration of 4–40 μg/ml was found to be greater than 0.999. The regression equation describing the absorbance versus concentration relationship is $A = 0.0113C + 0.0093$. Logarithmic plots (Fig. 1) of the residual concentration of olanzapine versus time are linear ($r > 0.98$) at all pH levels studied. The disappearance of olanzapine from aqueous solutions followed pseudo-first-order kinetics under the experimental conditions. The calculated pseudo-first-order rate constants at various pH values and temperature ($70.0 \pm 0.2\,^{\circ}C$) are listed in Table 1. The pH-rate profile for the hydrolysis of olanzapine at 70 °C is shown in Fig. 2. The profile was constructed from the logarithm of the observed pseudo-first-order rate constants and the corresponding pH values. The rate profile shows that the degradation of olanzapine is acid and base catalyzed. The linear portions of the curve have slopes close to negative unity and positive unity indicating that specific acid and base catalysis is occurring in this

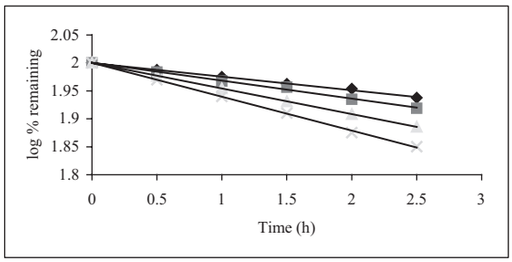

Fig. 1: Plot of logarithm of percent remaining of olanzapine versus time. Key: (■) pH 0.70; (■) pH 0.4; (▲) pH 0.20; (×) pH 0.10

pH region respectively. In the pH range studied, the reaction can be described by the following equation:

$$k_{obs} = k_H[H^+] + k_{OH}[OH^-] + k_o \quad (1)$$

where k_H and k_{OH} is the second-order rate constant for the hydrogen ion and hydroxide ion-catalyzed degradation respectively, k_o is the first-order rate constant of spontaneous or water catalyzed degradation, k_{obs} is the overall observed rate constant. The apparent first-order rate constant for water catalyzed, second-order rate constant for hydrogen ion and hydroxide ion catalyzed degradation were determined to be $5.75 \times 10^{-2}\,h^{-1}$,

Table 1: First-order rate constant of olanzapine in aqueous solution determined at $70 \pm 0.2\,^{\circ}C$

pH	Medium		k_{obs} $(h)^x$	$t_{1/2}$
	Composition	Concentration, M		
0.10	HCl	8.0×10^{-1}	0.1378 ± 1.35	5.03
0.20	,,	6.0×10^{-1}	0.1056 ± 0.86	6.56
0.40	,,	4.0×10^{-1}	0.0747 ± 3.34	9.27
0.70	,,	2.0×10^{-1}	0.0575 ± 1.91	12.05
13.30	NaOH	2.0×10^{-1}	0.1312 ± 0.99	5.28
13.60	,,	4.0×10^{-1}	0.3061 ± 0.39	2.26
13.80	,,	6.0×10^{-1}	0.3982 ± 0.45	1.74
13.9	,,	8.0×10^{-1}	0.4625 ± 0.50	1.50

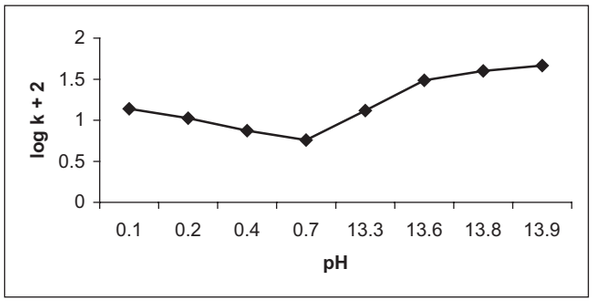

Fig. 2: Plot of logarithm of observed rate constant versus pH

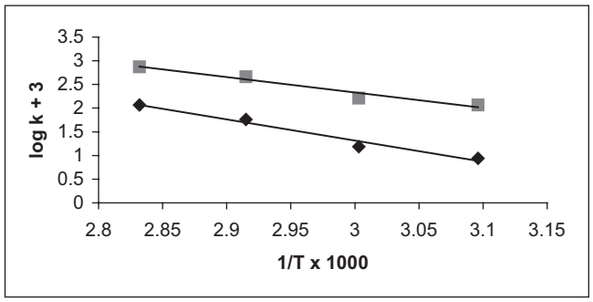

Fig. 3: Plot of logarithm of the observed rate constant versus reciprocal temperature. Key: (■) pH 0.70; (■) pH 13.90

$1.343 \times 10^{-1}\,mol^{-1}h^{-1}$ and $6.73 \times 10^{-11}\,mol^{-1}h^{-1}$ respectively. The k_o was obtained from the intersection of the acid and base catalyzed pH-rate profile plots while k_H and k_{OH} were obtained from the intercepts in the low and high pH regions respectively, of log (k_{obs}- k_o) versus pH plots. The effect of temperature on the hydrolytic reaction of olanzapine in solution was studied by measuring the pseudo-first-order rate constants at pH 0.70 and pH 13.90 respectively and at temperatures ranging from 50 to 80 °C. The results including other thermokinetic data are given in Table 2. A plot of the logarithm of the observed first-order rate constant against the reciprocal of the absolute temperature is shown in Fig. 3. The Arrhenius plots were linear ($r > 0.978$) indicating single degradation mechanism that justified the extrapolation of the results to obtain rate constants at 25 °C. The activation energy for the hydrolytic reaction was evaluated from the Arrhenius equation. The activation energies are 92.0 kJ/mol (pH 0.70) and 66.8 kJ/mol (pH 13.90) respectively. The estimated rate constants at 25 °C are 5.10×10^{-4} (pH 0.70) and 1.43×10^{-2} (pH 13.90) respectively. Using the rate constants at 25 °C, the frequency factors (A) were evaluated to be $7.27 \times 10^{11}\,h^{-1}$ (pH 0.70) and $1.49 \times 10^{9}\,h^{-1}$ (pH 13.90) respectively. The high values of the frequency factors indicate a large proportion of collisions between olanzapine molecules and hydrogen ion or hydroxide ion during the hydrolytic reaction.
The half-lives of degradation at 25 °C were calculated to be 57 days (pH 0.70) and 2 days (pH 13.90) respectively. To obtain further information from the kinetic investigation, the entropy of activation was calculated by substituting the values obtained for the activation energy and rate constants at 70 °C and pH 0.70 and 13.90 respectively, into the Eq. (2) (Dickson et al. 1971).

$$k = KT/h\, e^{-\Delta H/RT} \times \Delta S/R \qquad (2)$$

where k = rate constant at 70 °C and corresponding pH; K = Boltzman's constant; h = Planck's constant; R = gas constant; T in °K; ΔH = heat of activation; ΔS = entropy of activation. $\Delta H = E\text{-}RT$, where E = activation energy and the other terms have the same notation as above. At pH 0.70 and pH 13.90, ΔS was calculated to 1.25 J/mol/°C and 0.916 J/mol/°C respectively. In this study, no attempt was made to determine the degradation products and specific degradation pathways for olanzapine. However, as the TLC analysis and absorbance spectra show the degraded product to be more polar than olanzapine, the probable mechanism of reaction of acid catalyzed degradation involves protonation of the sulphur atom of the thieno moiety, followed by the rupture of the C-S bond adjacent to diazepine ring. For base catalyzed degradation, the mechanism could involve proton transfer from the secondary amine in the benzodiazepine ring to the sulfur atom, followed by electron delocalization and subsequent cleavage of the C-S bond.
In conclusion, the observed degradation reaction rates followed first-order rate kinetics. The pH-rate profile reveals specific acid-base catalysis. Olanzapine is more stable in acidic solution. Finally, the investigation suggests that at 25 °C and pH 0.70, olanzapine exhibits a half-life of 57 days.

3. Experimental

3.1. Materials

Olanzapine (Sun Pharmaceuticals Inc., India). All other chemicals are of analytical grade.

3.2. Apparatus

Ultraviolet/Visible spectrophotometer (UV 2102 PC, Unico) was used to measure the absorbance readings. pH measurement was performed with Orion pH meter, model 5A, 520 with combination glass electrode.

3.3. Standard solution

Stock solution of olanzapine (400 µg/ml) was prepared in methanol. Aliquots of the standard stock solution were pipetted into a 10 ml volumetric flask and diluted to volume with methanol to give final concentration of 4-40 µg/ml. Absorbance readings were taken at a maximum wavelength of 275 nm.

Table 2: Effect of temperature on the first-order rate constant of olanzapine in aqueous solution

pH	k_{obs} (h^{-1})^x					E_a (kJ mol^{-1})
	25 °C	50 °C	60 °C	70 °C	80 °C	
0.10	0.0044	0.0345 ± 3.6	0.0598 ± 2.0	0.1378 ± 1.3	0.2387 ± 0.12	67.3
0.20	0.0026	0.0241 ± 1.8	0.0361 ± 3.8	0.1056 ± 0.86	0.1799 ± 0.24	71.8
0.40	0.0008	0.0120 ± 7.1	0.0289 ± 4.8	0.0747 ± 3.3	0.1655 ± 0.48	89.4
0.70	0.0005	0.0087 ± 6.3	0.0153 ± 5.1	0.0575 ± 1.9	0.1160 ± 1.4	92.0
13.30	0.0028	0.0276 ± 1.1	0.0523 ± 1.5	0.1312 ± 2.3	0.2484 ± 1.7	76.1
13.60	0.0046	0.0587 ± 3.1	0.0774 ± 1.3	0.3061 ± 0.40	0.5231 ± 0.19	80.3
13.80	0.0068	0.0788 ± 1.6	0.1234 ± 0.38	0.3982 ± 0.45	0.7166 ± 2.1	66.8
13.9	0.0143	0.1170 ± 1.3	0.1623 ± 0.78	0.4625 ± 1.4	0.7459 ± 0.58	62.9

3.4. Kinetic procedure

Olanzapine was dissolved in methanol to give concentration of 1.28×10^{-3} M. This was used as the stock solution. For stability tests, the stock solution was diluted with acidic or basic solution of the appropriate strength up to a concentration of 1.28×10^{-4} M. A constant ionic strength of 1.0 was maintained for each solution by adding an appropriate amount of NaCl. The solution was filled into a 10 ml flask and then stored in a constant water bath maintained at $70 \pm 0.2\,^{\circ}$C. At appropriate intervals, the flasks were taken from the bath, cooled and the solutions were analyzed. The degradation was followed by monitoring the absorbance at 275 nm and determination was done in triplicate.

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