Olanzapine degradation kinetics in aqueous solution

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Olanzapine degradation kinetics in aqueous solution

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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-1-(4-methyl-1-piperazinyl)-10H-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-HT2), muscarinic, histamine (H1) and adrenergic (α1) receptors as well as dopamine (D1/D2) 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 were linear (r > 0.98) at all pH levels studied. The disappeareance 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 ± 0.2 °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

![Figure 1: Plot of logarithm of percent remaining of olanzapine versus time. Key: ■ pH 0.20; □ pH 0.4; △ pH 0.6; ○ pH 0.8; ▲ pH 1.0.](attachment:image)

![Figure 2: pH-rate profile for the hydrolysis of olanzapine at 70°C.](attachment:image)

Table 1: First-order rate constant of olanzapine in aqueous solution determined at 70 ± 0.2 °C

<table>
<thead>
<tr>
<th>pH</th>
<th>Medium</th>
<th>kobs (h⁻¹)</th>
<th>T/°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.20</td>
<td>HCl</td>
<td>0.1378 ± 0.135</td>
<td>5.03</td>
</tr>
<tr>
<td>0.40</td>
<td></td>
<td>0.1056 ± 0.086</td>
<td>6.56</td>
</tr>
<tr>
<td>0.70</td>
<td></td>
<td>0.0742 ± 0.034</td>
<td>9.27</td>
</tr>
<tr>
<td>1.00</td>
<td>NaOH</td>
<td>0.0575 ± 0.019</td>
<td>12.05</td>
</tr>
<tr>
<td>1.20</td>
<td></td>
<td>0.1312 ± 0.099</td>
<td>5.28</td>
</tr>
<tr>
<td>1.40</td>
<td></td>
<td>0.5001 ± 0.039</td>
<td>2.26</td>
</tr>
<tr>
<td>1.60</td>
<td></td>
<td>0.3982 ± 0.045</td>
<td>1.74</td>
</tr>
<tr>
<td>1.80</td>
<td></td>
<td>0.4625 ± 0.050</td>
<td>1.50</td>
</tr>
</tbody>
</table>

1.343 \times 10^{-1} \text{molL}^{-1} \text{s}^{-1} \text{and} \ 6.73 \times 10^{-1} \text{molL}^{-1} \text{s}^{-1} \text{respectively.} \ The \ k_2 \ was \ obtained \ from \ the \ intersection \ of \ the \ acid \ and \ base \ catalyzed \ pH-rate \ profile \ plots \ while \ k_0 \ and \ k_{OH} \ were \ obtained \ from \ the \ intercepts \ in \ the \ low \ and \ high \ pH \ regions \ respectively, \ of \ \log (k_{OH}-k_0) \ 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^\circ \ 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 \ \left( r > 0.978 \right) \ indicating \ single \ degradation \ mechanism \ that \ jus-
ified \ the \ extrapolation \ of \ the \ results \ to \ obtain \ rate \ constants \ at \ 25^\circ \ C. \ The \ activation \ energy \ for \ the \ hydrolytic \ reaction \ was \ evaluated \ from \ the \ Arrhenius \ equation. \ The \ activation \ energies \ are \ 92.0 \text{kJ/mol} \ \text{(pH 0.70)} \ and \ 66.8 \text{kJ/mol} \ \text{(pH 13.90)} \ respectively. \ The \ estimated \ rate \ constants \ at \ 25^\circ \ C \ are \ 5.10 \times 10^{-3} \ \text{(pH 0.70)} \ and \ 1.43 \times 10^{-2} \ \text{(pH 13.90)} \ respectively. \ Using \ the \ rate \ constants \ at \ 25^\circ \ C, \ the \ frequency \ factors \ \left( A \right) \ were \ evaluated \ to \ be \ 7.27 \times 10^{11} \ \text{h}^{-1} \ \text{(pH 0.70)} \ and \ 1.49 \times 10^{12} \ \text{h}^{-1} \ \text{(pH 13.90)} \ respectively. \ The \ high \ values \ of \ the \ frequency \ factors \ indicate \ a \ large \ proportion \ of \ collisions \ between \ olanzapine \ molecules \ and \ hydroxide \ ion \ or \ hydroxide \ ion \ during \ the \ hydrolytic \ reaction. \ The \ half-lives \ of \ degradation \ at \ 25^\circ \ C \ were \ calculated \ to \ be \ 57 \ days \ \text{(pH 0.70)} \ and \ 2 \ days \ \text{(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^\circ \ C \ and \ pH \ 0.70 \ and \ 13.90 \ respectively, \ into \ the \ Eq. \ \left( 2 \right) \ \text{(Dickson et al. 1971)}.

\begin{equation}
\frac{\text{k}}{\text{k}_\text{T} \text{n}_\text{e}^{-\frac{\text{AE}}{\text{RT}}}} - \Delta S = \text{RT} \tag{2}
\end{equation}

where \ k = \text{rate} \ \text{constant} \ \text{at} \ 70^\circ \ C \ \text{and} \ \text{corresponding} \ \text{pH}; \ K = \text{Boltzman’s} \ \text{constant}; \ T = \text{gas} \ \text{constant}; \ T \ \text{in} \ \text{K}; \ \Delta \text{H} = \text{heat} \ \text{of} \ \text{activation}; \ \Delta S = \text{entropy} \ \text{of} \ \text{activation}. \ \text{AE} = \text{E} - \text{RT, where E} = \text{activation} \ \text{energy} \ \text{and} \ \text{the} \ \text{other} \ \text{terms} \ \text{have} \ \text{the} \ \text{same} \ \text{notation} \ \text{as} \ \text{above.} \ \text{At} \ \text{pH} \ 0.70 \ \text{and} \ \text{pH} \ 13.90, \ \Delta S \ \text{was} \ \text{calculated} \ \text{to} \ 1.25 \text{J/mol}^\circ \text{C} \ \text{and} \ 0.96 \text{J/mol}^\circ \text{C} \ \text{respectively.} \ \text{In} \ \text{this} \ \text{study,} \ \text{no} \ \text{attempt} \ \text{was} \ \text{made} \ \text{to} \ \text{determine} \ \text{the} \ \text{degradation} \ \text{products} \ \text{and} \ \text{specific} \ \text{degradation} \ \text{pathways} \ \text{for} \ \text{olanzapine.} \ \text{However, as the TLC analysis and absorbance spec-
tra show the degraded product to be more polar than olanzapine, the probable mechanism of reaction of acid catalyzed degra-
dation involves protonation of the sulphur atom of the thieno \text{moety, followed by the rupture of the C-S bond adjacent to
}\ \text{diazepine ring.} \ \text{For} \ \text{base} \ \text{catalyzed} \ \text{degradation, the mechanism could involve proton transfer from the secondary amine in the
benzodiazepine ring to the sulfur atom, followed by electron \text{delocalization and subsequent cleavage of the S-C bond.}
}\ \text{In} \ \text{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.}
\text{Finally, the investigation suggests that at} \ 25^\circ \ C \ \text{and} \ \text{pH} \ 0.70, \ \text{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

Ultrasensitive/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 10ml 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 270 nm.

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

<table>
<thead>
<tr>
<th>pH</th>
<th>k_{OH} (s^{-1})</th>
<th>k_{k} (s^{-1})</th>
<th>k_{b} (s^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10</td>
<td>0.0044</td>
<td>0.0345 ± 3.6</td>
<td>0.0598 ± 2.0</td>
</tr>
<tr>
<td>0.20</td>
<td>0.0026</td>
<td>0.0241 ± 1.8</td>
<td>0.0361 ± 3.8</td>
</tr>
<tr>
<td>0.40</td>
<td>0.0008</td>
<td>0.0202 ± 7.1</td>
<td>0.0289 ± 4.8</td>
</tr>
<tr>
<td>0.70</td>
<td>0.0005</td>
<td>0.0087 ± 6.3</td>
<td>0.0153 ± 5.1</td>
</tr>
<tr>
<td>1.00</td>
<td>0.0029</td>
<td>0.0276 ± 1.1</td>
<td>0.0523 ± 1.5</td>
</tr>
<tr>
<td>1.30</td>
<td>0.0019</td>
<td>0.0087 ± 3.1</td>
<td>0.0289 ± 1.3</td>
</tr>
<tr>
<td>1.30</td>
<td>0.0004</td>
<td>0.0788 ± 1.6</td>
<td>0.1234 ± 0.38</td>
</tr>
<tr>
<td>1.30</td>
<td>0.0143</td>
<td>0.1170 ± 1.3</td>
<td>0.1623 ± 0.78</td>
</tr>
</tbody>
</table>

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3.4. Kinetic procedure

Olanzapine was dissolved in methanol to give concentration of \(1.28 \times 10^{-3}\) 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 \(1.28 \times 10^{-4}\) 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 ± 0.2 °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.

References


