1. A patient was given a 200 mg i.v. bolus of a drug. The following data was obtained.

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Conc. (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>12</td>
<td>0.5</td>
</tr>
</tbody>
</table>

a. Determine if the drug is eliminated by a zero-order or first-order process? Why?

Elimination by a first-order process because the log concentration vs. time plot is linear.

b. Calculate the elimination rate constant and half-life.

See graph above. The slope of the trend line is 0.4746, thus $k_e$ is $0.475 \text{ hr}^{-1}$.

$t_{1/2} = \frac{0.693}{0.475} = 1.46 \text{ hr}$

or can solve by:

$k_e = \frac{\ln C_2 - \ln C_1}{t_1 - t_2} = \frac{\ln 100 - \ln 0.5}{12 - 1} = \frac{5.29}{11} = 0.482 \text{ hr}^{-1}$

t_{1/2} = \frac{0.693}{0.482} = 1.44 \text{ hr}$

c. Determine the initial plasma concentration.

$C = C_0 \times e^{-k_e \cdot t}$

$C_0 = \frac{C}{e^{-k_e \cdot t}} = \frac{20}{e^{-0.475 \cdot 4}} = 133.7 \text{ mg} / L$
d. Calculate the volume of distribution.

\[
V_d = \frac{Dose}{C_0} = \frac{200 \text{ mg}}{133.7 \text{ mg/L}} = 1.50 \text{ L}
\]

e. Find the \(AUC_{0\to\infty}\) using the trapezoidal method.

\[
AUC_{0\to\infty} = \sum \left( \frac{C_n + C_{n+1}}{2} \times (t_{n+1} - t_n) \right)
\]

\[
AUC_{t\to \infty} = \frac{C_{\text{last}}}{k_e}
\]

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Conc. (mg/L)</th>
<th>AUC mg/L *hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>133.7</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>100</td>
<td>117</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>28</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>12</td>
<td>0.5</td>
<td>7</td>
</tr>
<tr>
<td>inf.</td>
<td></td>
<td>1.04</td>
</tr>
<tr>
<td>sum</td>
<td></td>
<td>309.04</td>
</tr>
</tbody>
</table>

2. Given that a lipophilic drug will readily enter tissue, state how the volume of distribution will change under the following conditions. If not mentioned, assume the other parameters to be fixed.

a. \(f_u\) decreases

\[
V_p(\leftrightarrow) + V_i(\leftrightarrow) \frac{f_u(\downarrow)}{f_{u,t}(\leftrightarrow)} = V_d(\downarrow)
\]

b. \(f_{u,t}\) increases

\[
V_p(\leftrightarrow) + V_i(\leftrightarrow) \frac{f_u(\leftrightarrow)}{f_{u,t}(\uparrow)} = V_d(\downarrow)
\]

c. Both \(f_u\) and \(f_{u,t}\) decrease by half

\[
V_p(\leftrightarrow) + V_i(\leftrightarrow) \frac{f_u(\downarrow)}{f_{u,t}(\downarrow)} = Vd(\leftrightarrow)
\]

d. \(f_u\) decreases and \(f_{u,t}\) increases

\[
V_p(\leftrightarrow) + V_i(\leftrightarrow) \frac{f_u(\downarrow)}{f_{u,t}(\uparrow)} = Vd(\downarrow)
\]
3. Drug X follows linear one-compartment pharmacokinetics, with a $t_{1/2} = 5.3$ hours and a $V_d = 21$ L, calculate a suitable i.v. bolus dose to achieve plasma concentrations of 3 mg/L for 12 hours. What is the initial plasma concentration?

\[
k_e = \frac{0.693}{5.3\ hr} = 0.13\ hr^{-1}
\]

\[
C = C_0 * e^{-k_e*t}
\]

\[
C_0 = \frac{C}{e^{-k_e*t}}
\]

\[
C_0 = \frac{3\ mg/L}{e^{-0.13*12}} = \frac{3\ mg/L}{0.21} = 14.3\ mg/L
\]

**Dose** = $C_0 * Vd = 14.3\ mg/L * 21\ L = 300.3\ mg \approx 300\ mg$
4. Identify which of the graphs below exhibits zero-order and first-order elimination. For which elimination is the half-life dependent on concentration? Write the equations and explain.

The plot on the left shows first-order elimination because it is a semi-log plot that results in a straight line.

\[ C = C_0 \cdot e^{-kt}, \quad C = \frac{C_0}{2} \text{ at } t = t_{1/2} \]

\[ \frac{C_0}{2} = C_0 \cdot e^{-k \cdot t_{1/2}} \]

\[ \frac{1}{2} = e^{-k \cdot t_{1/2}} \]

\[ \ln 2 = k \cdot t_{1/2} \]

\[ t_{1/2} = \frac{\ln 2}{k} \quad \therefore \text{half-life is independent on concentration.} \]

The plot on the right shows zero-order elimination because the plot on linear scale results in a straight line.

\[ C - C_0 = -k \cdot t \]

\[ C = C_0 - k \cdot t, \quad C = \frac{C_0}{2} \text{ at } t = t_{1/2} \]

\[ \frac{C_0}{2} = C_0 - k \cdot t_{1/2} \]

\[ t_{1/2} = \frac{C_0 - \frac{C_0}{2}}{k} \]

\[ t_{1/2} = \frac{C_0}{2 \cdot k} \quad \therefore \text{half-life is dependent on concentration.} \]