CHAPTER VII

PHARMACOKINETIC EVALUATION OF PIOGLITAZONE FLOATING TABLETS FORMULATED EMPLOYING OLIBANUM, CROSS-LINKED STARCH UREA AND HPMC K15M

Pharmacokinetic evaluation was done on pioglitazone floating tablets formulating employing olibanum, cross-linked starch urea and HPMC K15M as matrix formers in comparison to pioglitazone pure drug in rabbits with a view to evaluate the in vivo performance of the two new polymers proposed for floating tablets. Both pioglitazone pure drug and its floating tablets were tested at a dose of 10 mg in rabbits. For this purpose floating tablets (100 mg) each containing 10 mg of pioglitazone were prepared employing (i) olibanum, (ii) cross-linked starch urea and (iii) HPMC K15M as matrix formers at 50% strength in the formulae and sodium bicarbonate (15%) as gas generating agent, bees wax (15%) and ethyl cellulose (5%) as floating enhancers. These formulations are similar to floating tablet formulations PF7, PF8, and PF9 respectively. These prepared tablets remained floating over 48 h after a floating lag time 4-5 minutes.

EXPERIMENTAL

The following products were tested for in vivo pharmacokinetic evaluation.

(i) Pioglitazone (10 mg) (Product A)

(ii) Pioglitazone (10 mg) floating tablets formulated employing olibanum (50%) as matrix former, sodium bicarbonate (15%) as gas generating agent, bees wax (15%) and ethyl cellulose (5%) as floating enhancers, (Product B)

(iii) Pioglitazone (10 mg) floating tablets formulated employing cross-linked starch urea (50%) as matrix former, sodium bicarbonate (15%) as gas generating agent, bees wax (15%) and ethyl cellulose (5%) as floating enhancers, (Product C)
(iv) Pioglitazone (10mg) floating tablets formulated employing HPMC K15M (50%) as matrix former, sodium bicarbonate (15%) as gas generating agent, bees wax (15%) and ethyl cellulose (5%) as floating enhancers, (Product D).

**In vivo study protocol:**

The study was conducted as a crossover RBD in healthy rabbits of either sex (n = 6) with a washout period of one month. The *in vivo* protocols were approved by Institutional Animal Ethics Committee (No. 516/01/a/CPCSEA).

Healthy rabbits of either sex weighing 1.5 – 2.5 Kg were fasted over night. The products were administered at a dose of 10 mg of Pioglitazone.

After collecting the zero hour blood sample (blank), the product in the study was administered orally with 10 ml of water. Blood samples (1.0 ml) were collected from marginal ear vein at 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20 and 24 h after administration. Samples were collected in heparinised tubes and were centrifuged at 10,000 rpm for 10 min. The plasma separated was collected into dry tubes and the samples were stored under refrigerated conditions prior to assay for pioglitazone. Assay of the samples was done on the same day.

Plasma concentrations of pioglitazone were determined by the HPLC method developed by Chowdary, K.P.R. and Ghalib, V.¹ as described in Chapter V.

Plasma pioglitazone concentrations estimated following the oral administration of pioglitazone and its floating tablets are given Table 7.1 and shown in Fig.7.1. From the time Vs plasma concentration data various pharmacokinetic parameters such as peak concentration (C<sub>max</sub>), time at which peak occurred (T<sub>max</sub>), area under the curve (AUC),
elimination rate constant (K_{el}), biological half-life (t_{1/2}), percent absorbed to various times and absorption rate constant (K_a) were calculated in each case as per known standard methods. The results are given in Table 7.2.

**DETERMINATION OF PHARMACOKINETIC PARAMETERS**

**Determination of C_{max} and T_{max}:**

From the time versus plasma concentration curves, peak plasma concentration (C_{max}) and time at which peak occurred (T_{max}) were recorded.

**Determination of Elimination Rate Constant (K_{el}) and Biological half-life (t_{1/2}):**

Time versus plasma concentration data was plotted on a semi logarithmic graph paper. The elimination rate constant (K_{el}) was calculated from the slope of the linear line in the elimination phase (the ‘best fit’ linear regression line for the points in the elimination phase was drawn by the method of least squares). The corresponding biological half-life was calculated using the equation,

\[ t_{1/2} = \frac{0.693}{K_{el}} \]

**Determination of Percentages Absorbed to Various Times and Absorption Rate Constant (K_a):**

Percentages absorbed to various times and absorption rate constant (K_a) were calculated from plasma concentration data by the method described by Wagner and Nelson^{2, 3}. The equation developed for the determination of absorption rate from blood data is
\[ \frac{dA}{dt} = V_d \cdot \frac{dC_b}{dt} + K_{el} \cdot C_b \]

Where, \( \frac{dA}{dt} \) = absorption rate, \( V_d \) = apparent volume of distribution \( \frac{dC_b}{dt} \) = rate of change of blood concentration \( C_b \) with respect to time \( t \) and \( K_{el} \) = elimination rate constant.

The equation may be integrated between the limits of \( t = 0 \) and \( t = T \) and divided by \( V_d \) to give,

\[ \frac{A_T}{V_d} = C_T + K_{el} \cdot \int_{t=0}^{t=T} C_b \, dt \]

\[ \frac{A_T}{V_d} = C_T + K_{el} \cdot [AUC]_{t=T}^{t=0} \]

where \( A_T \) = amount of drug absorbed to time \( T \), \( C_T \) = blood concentration at time \( T \) and the quantity under the integral sign is the area under the blood concentration versus time curve between the indicated limits. When the successive values of \( A_T / V_d \) are calculated, a maximum or asymptotic value \( [A_T/V_d]_\infty \) is obtained. The maximum asymptotic value is divided into successive values of \( A_T / V_d \) to yield percentage absorbed data i.e.,

\[ \frac{A_T/V_d}{[A_T/V_d]_\infty} \times 100 \] as a function of time

A graph of log percent unabsorbed Vs time (Figs. 7.2) is a linear plot, the slope of which is equal to \( -K_a / 2.303 \) from which \( K_a \) was calculated.
Estimation of Area under the Curve [AUC]:

The area under the time versus plasma concentration curve (AUC) for 12 hour period was estimated, from an arithmetic plot of time versus plasma concentration by applying trapezoidal rule. The remaining area from 12 hours to $\infty$ time was calculated using the following equation,

$$[\text{AUC}]_{12}^\infty = \frac{\text{concentration at } 12^{\text{th}} \text{ hour}}{K_{el}}$$

Then, $[\text{AUC}]_{0}^{\infty} = [\text{AUC}]_{0}^{12} + [\text{AUC}]_{12}^\infty$

Determination of Mean Residence Time:

The tendency of drugs and metabolites to remain in the body can be assessed by measuring the mean residence time (MRT). Assuming that the drug in the organs and elimination is always in equilibrium with drug in plasma, the mean residence time can be defined as the average amount of time spent by drug molecules in the body before being eliminated (under constant clearance conditions). If one considers time course of drug concentration in plasma as statistical distribution curve, it can be shown that

$$\text{MRT} = \frac{\text{AUMC}}{\text{AUC}}$$

Where the AUMC is the area under the ‘first movement curve’ and is obtained from a plot of the product of drug concentration in plasma and time versus time from zero to infinity.

$$\text{AUMC} = \int_{0}^{\infty} tC(t)dt$$
AUC is the area under the ‘zero’ moment curve and is obtained by plotting the drug concentration in plasma versus time (C vs. t) from zero to infinity.

\[ \text{AUC} = \int_{0}^{\infty} C(t) \, dt \]

The MRT is considered as the statistical movement analogy to the half-life (t_{1/2}).

Plots of time versus serum concentration (t vs. C) and time versus the product of concentration and time (t vs. Ct) were plotted and the area under the corresponding curves i.e. AUC and AUMC respectively were computed. The mean residence time (MRT) in each case calculated as follows:

\[ \text{MRT} = \frac{\text{AUMC}}{\text{AUC}} \]

A summary of the pharmacokinetic parameters estimated is given in Table 7.2
<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Plasma Concentration of Pioglitazone (μg/ml) (x ± s.d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>1.0</td>
<td>3.6 ± 0.12</td>
</tr>
<tr>
<td>2.0</td>
<td>5.2 ± 0.14</td>
</tr>
<tr>
<td>3.0</td>
<td>5.7 ± 0.19</td>
</tr>
<tr>
<td>4.0</td>
<td>5.4 ± 0.16</td>
</tr>
<tr>
<td>5.0</td>
<td>5.2 ± 0.19</td>
</tr>
<tr>
<td>6.0</td>
<td>4.9 ± 0.18</td>
</tr>
<tr>
<td>8.0</td>
<td>4.4 ± 0.12</td>
</tr>
<tr>
<td>10.0</td>
<td>3.8 ± 0.08</td>
</tr>
<tr>
<td>12.0</td>
<td>3.6 ± 0.11</td>
</tr>
<tr>
<td>16.0</td>
<td>2.7 ± 0.11</td>
</tr>
<tr>
<td>20.0</td>
<td>1.6 ± 0.60</td>
</tr>
<tr>
<td>24.0</td>
<td>0.9 ± 0.31</td>
</tr>
</tbody>
</table>

A: Pioglitazone; B: Floating Tablets with Olibanum; C: Floating Tablets with Cross-linked starch urea; D: Floating Tablets with HPMC K15M.
Fig. 7.1: Plasma Concentration of Pioglitazone Following the Oral Administration of Pioglitazone (A) and its Floating Tablets Formulated Employing Olibanum (B), Cross-linked starch urea (C) and HPMC K15m (D)
Fig. 7.2: Log Plasma Concentration Vs Time Plot Following the Oral Administration of Pioglitazone during the Elimination Phase for the Determination of $t_{1/2}$

$y = -0.0521x + 1.195$

$R^2 = 0.9826$
Table 7.2

Summary of Pharmacokinetic Parameters Estimated Following the Oral Administration of Pioglitazone and its Floating Tablets in Rabbits (n = 6)

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (μg/ml)</td>
<td>5.7±0.19</td>
<td>3.7±0.12</td>
<td>3.8±0.17</td>
<td>3.10±0.51</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>3</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>$K_{\text{el}}$ (h$^{-1}$)</td>
<td>0.1199</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>5.78</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>$(\text{AUC})_0^{24}$ (μg.h/ml)</td>
<td>78.92</td>
<td>74.17</td>
<td>68.15</td>
<td>55.68</td>
</tr>
<tr>
<td>$(\text{AUC})_0^\infty$ (μg.h/ml)</td>
<td>86.60</td>
<td>88.40</td>
<td>80.12</td>
<td>78.45</td>
</tr>
<tr>
<td>$K_a$ (h$^{-1}$)</td>
<td>1.462</td>
<td>0.133</td>
<td>0.225</td>
<td>0.1598</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>9.82</td>
<td>13.65</td>
<td>13.48</td>
<td>13.30</td>
</tr>
<tr>
<td>BA (%)</td>
<td>100</td>
<td>102.08</td>
<td>92.52</td>
<td>90.58</td>
</tr>
</tbody>
</table>

A: Pioglitazone; B: Floating Tablets with Olibanum; C: Floating Tablets with Cross-linked starch urea; D: Floating Tablets with HPMC K15M.
RESULTS AND DISCUSSION

Pharmacokinetic evaluation was done on pioglitazone floating tablets formulating employing olibanum, cross-linked starch urea as matrix formers in comparison to pioglitazone pure drug in rabbits with a view to evaluate the *in vivo* performance of the polymers proposed for floating tablets.

A summary of the pharmacokinetic parameters estimated following the oral administration of pioglitazone products tested is given in Table 7.2. The elimination rate constant ($K_{el}$) for pioglitazone was found to be $0.1199 \text{ h}^{-1}$ and the corresponding biological half life was found to be 5.78 h following the oral administration of pioglitazone. The $t_{1/2}$ value of pioglitazone obtained in the present work is in good agreement with the earlier reported value of 3-6 h. The mean residence time (MRT) was found to be 9.82 h. The absorption rate constant ($K_a$) was found to be $1.462 \text{ h}^{-1}$. A $C_{max}$ of $5.7 \pm 0.19 \text{ μg/ml}$ was observed at 3.0 h after oral administration of pioglitazone pure drug. A second peak concentration of $5.2 \pm 0.22 \text{ μg/ml}$ was observed at 6.0 h after administration. Later the plasma concentrations were decreased rapidly.

When the pioglitazone floating tablets were administered orally at the same dose of 10 mg, the plasma concentrations were found to be lower than those observed with pioglitazone pure drug (A) (Fig. 7.2) indicating slow absorption of pioglitazone from the floating tablets. A $C_{max}$ of $3.7 \pm 0.12 \text{ μg/ml}$, $3.8 \pm 0.17 \text{ μg/ml}$ and $3.1 \pm 0.51 \text{ μg/ml}$ was observed at 6.0 h following the oral administration of floating tablets B, C and D.
respectively. The absorption rate constant \( (K_a) \) was found to be \( 0.133 \, \text{h}^{-1} \), \( 0.225 \, \text{h}^{-1} \) and \( 0.1598 \, \text{h}^{-1} \) with floating tablets B, C and D respectively. The plasma concentrations were stabilized and maintained within a narrow range for longer periods of time in the case of floating tablets (Fig. 7.2). The mean residence time (MRT) was increased from 9.82 h for pioglitazone pure drug to 13.65 h, 13.48 h and 13.30 h respectively with the floating tablets B, C and D. The MRT value indicated longer stay of drug in the body when administered as floating tablets. Based on \( \text{AUC}_0^{\infty} \) the relative bioavailability of pioglitazone from the floating tablets was found to be 102.05 %, 92.52% and 90.58% respectively with floating tablets B, C and D when compared to pioglitazone pure drug (100 %).

The pharmacokinetic evaluation, thus, indicated that pioglitazone from the floating tablets formulated was released slowly and absorbed slowly over longer periods of time \textit{in vivo} resulting in the maintenance of plasma concentration within a narrow range over a longer period of time.

REFERENCES


