PHARMACOKINETIC EVALUATION OF DICLOFENAC MATRIX TABLETS FORMULATED EMPLOYING CROSS-LINKED STARCH UREA
CHAPTER IX
PHARMACOKINETIC EVALUATION OF DICLOFENAC MATRIX TABLETS FORMULATED EMPLOYING CROSS LINKED STARCH UREA

For evaluating the release retarding and rate controlling efficiency of cross linked starch urea in vivo, pharmacokinetic evaluation was done on diclofenac matrix tablets formulated employing cross linked starch urea in comparison to diclofenac pure drug in rabbits. Diclofenac matrix formulation was used as model formulation to evaluate the in vivo performance of cross linked starch urea. Both diclofenac pure drug and its matrix tablets were tested at a dose of 15 mg in rabbits. For this purpose matrix tablets each containing 15 mg of diclofenac were prepared employing cross linked starch urea at 50 % strength in the formula similar to diclofenac formulation DF3 described in Chapter VII, which gave slow and extended release of diclofenac over 24 hours comparable to that of commercial SR formulation.

EXPERIMENTAL

The following products were tested for in vivo pharmacokinetic evaluation.

1. Diclofenac (15 mg) pure drug
2. Diclofenac (15 mg) matrix tablets formulated employing cross linked starch urea (50 %) as release retardant.

In Vivo study protocol:

The study was conducted as a cross over 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 (Regd. 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 15 mg of diclofenac. After collecting the zero hour blood sample (blank), the product in the study was administered orally with 10 ml of water. Blood samples (3 ml) were collected from marginal ear vein at 0.5, 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 diclofenac content. Assay was performed on the same day.

Plasma concentrations of diclofenac were determined by an HPLC method developed by Chowdary, K. P. R. and Murali Krishna M. N. as described in Chapter V.

Plasma diclofenac concentrations estimated following the oral administration of diclofenac and its matrix tablets are given Table 9.1 and shown in Fig 9.1. From the time Vs plasma concentration data various pharmacokinetic parameters such as peak concentration (C_{max}), time at which peak occurred (T_{max}), area under the curve (AUC), elimination rate constant (k_e), 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 9.2.
DETERMINATION OF PHARMACOKINETIC PARAMETERS

**Determination of C\text{max} and T\text{max}**

From the time versus plasma concentration curves, peak plasma concentration (C\text{max}) and time at which peak occurred (T\text{max}) were recorded.

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

Time versus plasma concentration data were plotted on a semi logarithmic graph paper (Fig. 9.2). The elimination rate constant (k\text{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 Percentage Absorbed to various Times and Absorption Rate Constant (K_a)**

Percentages absorbed to various times and absorption rate constant (K\text{a}) were calculated from plasma concentration data by the method described by Wagner and nelson\textsuperscript{2,3}. The equation developed for the determination of absorption rate from blood data is

\[ \frac{dA}{dt} = V_d \frac{dC_b}{dt} + K_{a} C_b \]

Where \( \frac{dA}{dt} \) = Absorption rate, \( V_d \) = apparent volume of distribution, \( \frac{dC_b}{dt} \) = rate of change of blood concentration (C\text{b}) with respect to time t and K\text{a} = elimination rate constant.
The equation may be integrated between the limits of \( t = 0 \) and \( t = T \) and divided by \( V_d \) to give,

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

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

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 \([A_T/V_d]_a\) is obtained. The maximum asymptotic value is divided into successive values of \( A_T/V_d \) to yield percentage absorbed data i.e.,

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

A graph of log percent unabsorbed Vs time (Fig. 9.3) 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 24 hour period was estimated, from an arithmetic plot of time versus plasma concentration by applying trapezoidal rule. The remaining area from 24 hours to \( \alpha \) time was calculated using the following equation,

\[
[AUC]_{\alpha}^{24} = \text{concentration at 24th hour} / K_{el}
\]

Then, \([AUC]_{\alpha} = [AUC]_{24} + [AUC]_{\alpha}^{24}\)
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.

\[ \text{AUMC} = \int_0^\infty C(t) \, dt \]

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-time (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 was calculated as follows:

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

A Summary of the pharmacokinetic parameters estimated is given in Table 9.2.
Table 9.1

Plasma Concentrations of Diclofenac following the Oral Administration Diclofenac (A) and Diclofenac matrix Tablets Formulated Employing Cross linked Starch Urea (B) in rabbits (n = 6)

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Plasma Concentration of Diclofenac (µg/ml) x ± (s.d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>0.5</td>
<td>1.5 ± (0.5)</td>
</tr>
<tr>
<td>1.0</td>
<td>2.3 ± (0.6)</td>
</tr>
<tr>
<td>2.0</td>
<td>4.1 ± (1.2)</td>
</tr>
<tr>
<td>3.0</td>
<td>4.7 ± (1.4)</td>
</tr>
<tr>
<td>4.0</td>
<td>4.5 ± (1.6)</td>
</tr>
<tr>
<td>5.0</td>
<td>4.3 ± (1.0)</td>
</tr>
<tr>
<td>6.0</td>
<td>4.0 ± (1.2)</td>
</tr>
<tr>
<td>8.0</td>
<td>3.1 ± (0.8)</td>
</tr>
<tr>
<td>10.0</td>
<td>2.8 ± (1.0)</td>
</tr>
<tr>
<td>12.0</td>
<td>2.7 ± (0.6)</td>
</tr>
<tr>
<td>16.0</td>
<td>1.5 ± (1.2)</td>
</tr>
<tr>
<td>20.0</td>
<td>0.8 ± (0.8)</td>
</tr>
<tr>
<td>24.0</td>
<td>0.6 ± (0.4)</td>
</tr>
</tbody>
</table>
Fig 9.1: Plasma Concentration of Diclofenac Following the Oral Administration of Diclofenac (A) and Matrix Tablets Formulated Employing Crosslinked starch Urea (B) in Rabbits (n=6)
Fig. 9.2: Log Plasma Concentration Vs Time Plot Following the Oral Administration of Diclofenac during the Elimination Phase for the Determination of $t_{1/2}$
Fig. 9.3. Time Vs log percent unabsorbed Plots following Oral administration of Diclofenac pure Drug (O) and its Matrix tablets prepared employing Cross-linked Starch-Urea (●).

$y = -0.283x + 2.006$

$R^2 = 0.989$

$y = 0.051x + 2.016$

$R^2 = 0.974$

Fig. 9.3. Time Vs log percent unabsorbed Plots following Oral administration of Diclofenac pure Drug (O) and its Matrix tablets prepared employing Cross-linked Starch-Urea (●).
Table 9.2

Summary of Pharmacokinetic Estimated following the oral Administration of Diclofenac (A) and Diclofenac matrix tablets Formulated Employing Cross Linked Starch Urea (B) in rabbits (n = 6)

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (µg/ml)</td>
<td>4.7± (1.4)</td>
<td>2.9 ±(0.6)</td>
</tr>
<tr>
<td>T_{max} (h)</td>
<td>3.0</td>
<td>6.0</td>
</tr>
<tr>
<td>K_{el} (h^{-1})</td>
<td>0.1274</td>
<td>--</td>
</tr>
<tr>
<td>t_{1/2} (h)</td>
<td>5.44</td>
<td>--</td>
</tr>
<tr>
<td>(AUC)_{24}^0 (µg.h/ml)</td>
<td>56.17</td>
<td>60.15</td>
</tr>
<tr>
<td>(AUC)_{0}^a (µg.h/ml)</td>
<td>60.10</td>
<td>75.06</td>
</tr>
<tr>
<td>K_{a} (h^{-1})</td>
<td>0.8172</td>
<td>0.152</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>9.68</td>
<td>14.05</td>
</tr>
<tr>
<td>BA (%)</td>
<td>100</td>
<td>124.9</td>
</tr>
</tbody>
</table>
Results and Discussion

Pharmacokinetic evaluation was done on diclofenac matrix tablets formulated employing cross-linked starch-urea in comparison to diclofenac pure drug with a view to evaluate the release retarding and rate controlling efficiency of cross linked starch urea in vivo.

A summary of the pharmacokinetic parameters estimated following the oral administration of diclofenac products tested is given in Table 9.2.

The elimination rate constant \( (K_{el}) \) for diclofenac was found to be 0.1274 h\(^{-1}\) and the corresponding half life was found to be 5.44 h following the oral administration of diclofenac. The mean residence time (MRT) was found to be 9.68 h. The adsorption rate constant \( (K_a) \) was found to be 0.8172 h\(^{-1}\). A \( C_{\text{max}} \) of 4.7 ± 1.4 µg/ml was observed at 3.0 h after oral administration of diclofenac pure drug. Later the plasma concentrations were decreased rapidly.

When the diclofenac matrix tablets formulated employing cross linked starch urea were administrated orally at the same dose of 15 mg, the plasma concentrations were found to be lower than those observed with the diclofenac pure drug (Fig. 9.1) indicating slow absorption of diclofenac from the matrix tablets. A \( C_{\text{max}} \) of 2.9 ± 0.6 µg/ml was observed at 6.0 h following the oral administration of matrix tablets. The absorption rate constant \( (K_a) \) was found to be 0.152 h\(^{-1}\). The plasma concentrations were stabilized and maintained within a narrow range for longer periods of time in the case of matrix tablets (Fig. 9.1). The mean residence time (MRT) was increased from 9.68 h for diclofenac pure drug to 14.05 h with the matrix tablets. The MRT value indicated longer stay of drug in the body when administered as matrix tablets. Based on \( \text{AUC}_{0}^{\infty} \) the relative bioavailability of diclofenac from cross linked starch urea matrix tablets was found to be 124.9 % when compared to diclofenac pure drug (100 %).
The pharmacokinetic evaluation, thus, indicated that diclofenac from the matrix tablets formulated employing cross-linked starch urea was released slowly and absorbed slowly over longer periods of time \textit{in vivo} resulting in the maintenance of plasma concentrations within a narrow range over longer periods of time. As such cross linked starch urea exhibited good release retarding and rate controlling effect \textit{in vivo} in the pharmacokinetic evaluation.
REFERENCES

