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Research Article

IN-VIVO PHARMACOKINETIC STUDIES OF SOLID DISPERSIONS OF CELECOXIB

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ABSTRACT

Dissolution rate and dissolution efficiency of poorly soluble non-steroidal anti inflammatory drugs (NSAIDs) could be markedly enhanced by solid dispersion technology. Solid dispersions of celecoxib (C) are subjected to *in vivo* pharmacokinetic evaluation to evaluate whether these systems improve oral bio availability of the celecoxib. All the pharmacokinetic parameters of absorption, namely K_a , C_{max} , T_{max} , percent absorbed to various times and AUC indicated rapid absorption and higher bioavailability of celecoxib when administered as its solid dispersions. The absorption rate constant (K_a) was found to be 3.5526hr^{-1} in the case of celecoxib-Croscarmellose-Poly vinyl pyrrolidone (C-CC-PVP) solid dispersion. Whereas in the case of celecoxib K_a was only 0.412hr^{-1} . An increase of 8.6 fold in K_a was observed with celecoxib-CC-PVP solid dispersion. AUC (extent of absorption) was also much higher in the case of celecoxib -CC-PVP solid dispersion when compared to celecoxib. $[AUC]_{0-12h}$ was increased from 91.54 ng-hr/ml for celecoxib to 587.13 ng-hr/ml for celecoxib-CC-PVP solid dispersion. Both K_a and AUC were markedly increased by CC-PVP solid dispersion. Thus, the results of pharmacokinetic studies indicated rapid and higher oral absorption of celecoxib when administered as CC-PVP solid dispersion.

Key Words: Dissolution Rate, Rate of Absorption, Solid dispersion.

INTRODUCTION

Non steroidal anti inflammatory drugs, are drugs with analgesic, antipyretic and anti-inflammatory effects. They reduce pain, fever and inflammation. Most of the NSAIDs belong to class II category under Biopharmaceutical Classification System (BCS) i.e., they are inherently highly permeable through biological membranes, but exhibit low aqueous solubility. They need enhancement in solubility and dissolution rate for improving their oral bio availability. Among the various methods for improving the dissolution rate and bioavailability, solid dispersion technology is more efficient and industrially accepted method for improving the dissolution rate and bioavailability of the selected NSAIDs. As a consequence of the solid dispersions process using super disintegrants and hydrophilic polymers many physico chemical properties, such as solubility, dissolution rate stability and bioavailability can be favorably affected¹. Celecoxib (C), 4-[5-(4-methylphenyl)-3- (trifluoromethyl)-1H-pyrazol-1-yl] benzene sulfonamide is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic and anti-pyretic activities in human models. It is used in the treatment of rheumatoid arthritis and osteoarthritis². Celecoxib is also used in the management of acute pain and dysmenorrhoea. Celecoxib is absorbed slowly from the gastrointestinal tract, peak plasma concentrations³ being achieved approximately 4hrs after an oral dose.

MATERIALS AND METHODS

Healthy rabbits of either sex (weighing 1.5-2.5 kg) were fasted overnight. Celecoxib and its solid dispersions were administered at dose equivalent to 10 mg/kg of celecoxib. Each product was repeated 6 times (n=6). The in vivo experiments were conducted as per the following crossover RBD. A washout period of one month was given between the treatments. After collecting the zero hour blood sample (blank), the product in the study was administered orally in a capsule shell with 10 ml of water. Blood samples (3 ml) were collected from marginal ear vein at 0.25, 0.5, 1.0, 2.0,

3.0, 4.0, 6.0, 8.0 and 12.0 h after administration. The blood samples were allowed to clot and centrifuged at 5000 rpm and the serum separated was collected into dry tubes. All the samples were stored under refrigerated conditions prior to assay. Serum concentration of drug (celecoxib) was determined by the HPLC method.

Estimation of Celecoxib Serum Samples

Celecoxib in serum samples was estimated according to High Performance Liquid Chromatographic (HPLC) method⁴.

Materials

1. Celecoxib (Gift sample from Ipca Laboratories, Mumbai)
2. Ketoprofen (Gift sample from Dr.Reddy's Laboratories, Hyderabad)
3. Acetonitrile (HPLC grade, Qualigens)
4. Methanol (HPLC grade, Qualigens)
5. Glacial acetic acid (Excelar, Qualigens)

Chromatographic conditions

Instrument : A gradient high pressure liquid chromatograph (Shimadzu)
Column : C-18 RP (ODS-A) 250 x 4.6 mm I.D; Particle size : 5 µm
Mobile phase : Acetonitrile: water (55:45 v/v), pH adjusted to 2.95 with
glacial acetic acid
Flow rate : 1.5 ml/min
Injection volume : 20 µl
Detector : UV-VIS Spectrophotometric detector at 254 nm

Extraction Procedure

To 50 µl of internal standard (ketoprofen, 5 µg/ml in methanol) and 4.45 ml of methanol was added and the tubes were vortex-mixed for 15 min and centrifuged at 5000 rpm for 10 min. The supernatant was transferred to clean tubes and evaporated to dryness. The residue was reconstituted with 0.5 ml mobile phase and 20 µl of the solution was injected into the HPLC system after filtering through 0.2 µ nylon membrane filter.

Calibration Curve

Standard solutions containing 0.5, 1.0, 2.0, 3.0 and 4.0 µg/ml of Celecoxib were prepared in methanol. To each 50 µl of standard solution, 50 µl of internal standard (ketoprofen, 5 µg/ml in methanol), 500 µl of blank serum and 4.4 ml of methanol were added and the tubes processed as above. Standard curve was obtained by plotting peak area ratio of Celecoxib to internal standard vs. concentration. The results are given in Table 1 and Fig.1.

The serum concentration data following the administration of various products are given in Table 2 and shown in Fig. 2. From the time versus serum 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_{el}), biological half-life ($t_{1/2}$), percent absorbed to various times and absorption rate constant (K_a) were calculated in each case. The results are given in Table 3.

Table 1: Calibration Curve for the Estimation of Celecoxib in Serum byH PLC

Amount of (ng) Celecoxib added to 1.0 ml serum	Mean (n=5) ratio of peak area of Celecoxib to peak area of internal standard	Coefficient of variation (%)
50	0.422	1.09
100	0.849	1.24
200	1.681	0.98
300	2.504	0.86
400	3.410	1.18

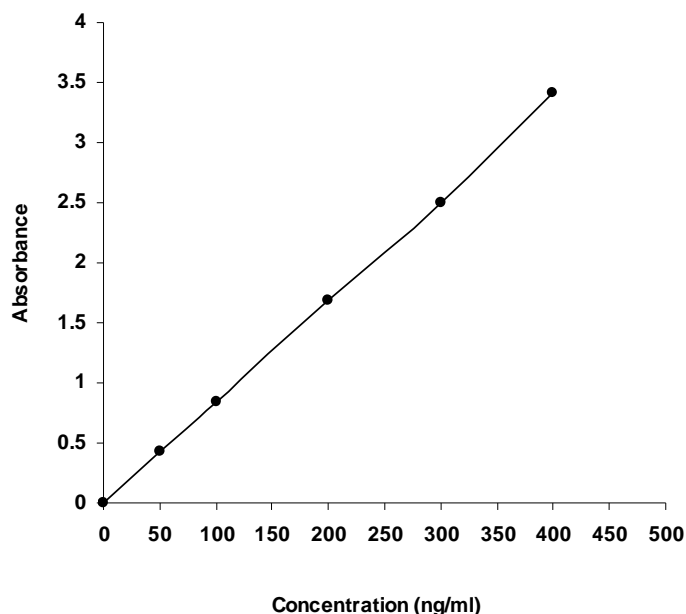


Fig 1. Calibration Curve for the Estimation of Celecoxib in Serum by HPLC

Table 2: Serum Concentration of Celecoxib and its Products following their Oral Administration in Rabbits (n=6)

Time (hrs)	Serum Concentration (ng/ml) of Celecoxib ($\bar{x} \pm s.d.$)	
	Celecoxib	Celecoxib-CC-PVP
0.25	2.7±1.1	64.4±12.1
0.50	4.6±1.2	74.2±14.3
1.0	6.7±2.1	76.1±10.6
2.0	8.2±2.6	72.8±15.1
3.0	10.2±2.9	67.1±12.7
4.0	12.4±3.3	62.7±11.7
6.0	9.5±3.9	48.5±12.7
8.0	7.1±3.2	38.5±10.4
12.0	3.6±3.6	19.2±8.5

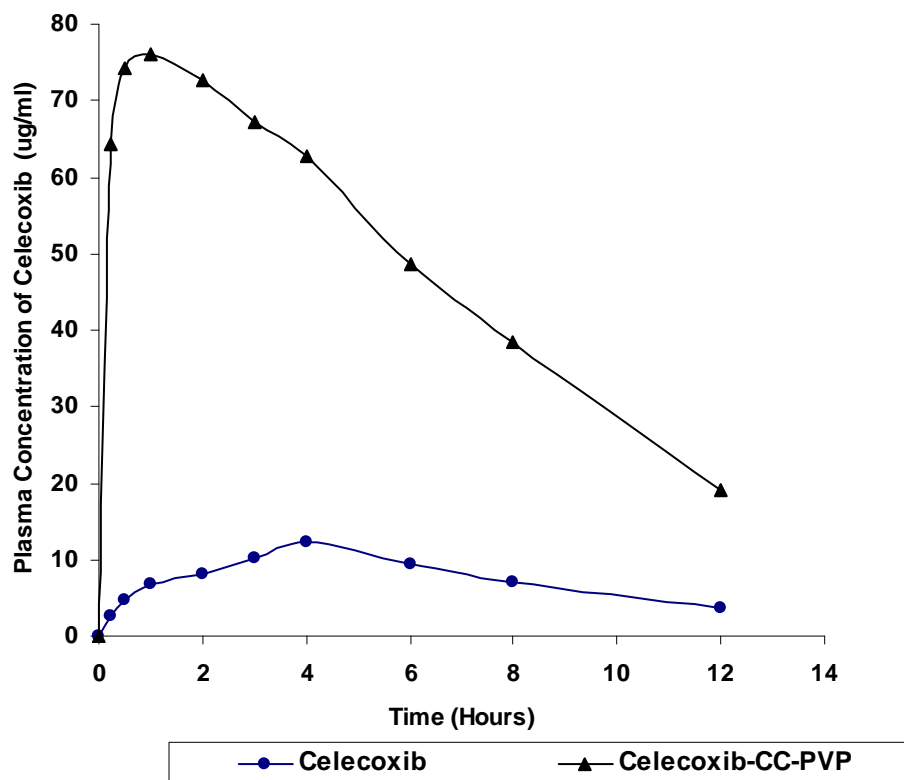


Fig. 2 Determination of Various Pharmacokinetic Parameters

Determination of C_{max} and T_{max}

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

Determination of Elimination Rate Constant (K_{el}) and biological Half-life ($t_{1/2}$)

Time versus 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 point in the elimination phase was drawn by the method of least squares). The corresponding biological half life is calculated using equation $t_{1/2} = 0.693/K_{el}$.

Determination of Percentages Absorbed To Various Times and Absorption Rate Constant (K_a)

Percentage absorbed to various times and absorbed rate constant (K_a) were calculated from serum concentration data by the method described by Wagner and Nelson^{1,2}. The equation developed for the determination of absorption rate fro blood data is

$$\frac{dA}{dt} = Vd \cdot \frac{dcb}{dt} + K_{el}.cb$$

Where, dA/dt = absorption rate, Vd = apparent volume of distribution,

dCb/dt = rate of change of blood concentration (Cb) at time t and

K_{el} = elimination rate constant.

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

$$\frac{At}{Vd} = C_T + K_{el} \cdot \int_{t=0}^{t=T} cbdt$$

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

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 are 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 by the successive values of A_T / V_d to yield percentage absorbed data i.e.

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

When a semilogarithmic plot of percentage unabsorbed versus time was drawn, straight line (the 'best fit' linear regression line was drawn by the method of least squares) is obtained, the slope of

which was equal to $-K_e/2.303$. The absorption rate constant (K_a) is calculated from the slope of this line.

Estimation of Area Under the Curve (AUC)

The area under the time versus serum concentration curve (AUC) for 24 hr period is estimated, from an arithmetic plot of time versus serum concentration by applying trapezoidal rule. The remaining area from 24 hrs to ∞ time was calculated using the following equation.

$$[AUC]_{12hr}^{\infty} = \frac{\text{Concentration at 12 hr}}{K_{el}}$$

$$\text{Then } [AUC]_0^{\infty} = [AUC]_0^{12hr} + [AUC]_{12hr}^{\infty}$$

Determination of C_{max} and T_{max}

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

RESULTS AND DISCUSSION

Pharmacokinetics of Celecoxib and its Products

Pharmacokinetic parameters estimated following the oral administration of celecoxib and its products are given in Table 3. The elimination rate constant (K_{el}) for celecoxib was found to be 0.1618 hr^{-1} and the corresponding biological half life ($t_{1/2}$) value of celecoxib obtained in the present study is in good agreement with earlier reported value of 4.33 hr. The absorption rate constant (K_a) was found to be 0.412 hr^{-1} following the oral administration of celecoxib. Celecoxib was found to be absorbed slowly when given orally and a peak serum concentration (C_{max}) of 12.45 ng/ml was observed at 4.0 hr following administration. All the pharmacokinetic parameters of absorption

(Table 3) namely K_a , C_{max} , T_{max} , percent absorbed to various times and AUC indicated rapid absorption and higher bioavailability of celecoxib when administered as its solid dispersion. Higher C_{max} and shorter T_{max} values were observed with these products when compared to those of celecoxib as such. The absorption rate constant (K_a) was found to be 3.552 hr^{-1} in the case of celecoxib-CC-PVP solid dispersion. Where as in the case of celecoxib, K_a was only 0.412 hr^{-1} . An increase of 8.6 fold in K_a was observed with celecoxib-CC-PVP solid dispersion. AUC (extent of absorption) was also much higher in the case of celecoxib solid dispersion when compared to celecoxib. $[AUC]_{0-12h}$ was increased from 91.54 ng-hr/ml for celecoxib to 587.13 ng-hr/ml for celecoxib solid dispersion. Thus, the results of pharmacokinetic studies indicated rapid and higher oral absorption of celecoxib when administered as its solid dispersion. Both K_a and AUC were markedly increased by solid dispersion with CC-PVP.

Table 3. Summary of Pharmacokinetic Parameters Estimated Following Oral Administration of Celecoxib and its Solid dispersion

Parameter	Celecoxib	Celecoxib-CC-PVP
C_{max} (ng/ml)	12.1	76.1
T_{max} (hr)	4.28	1.00
K_{el} (hr^{-1})	0.161	0.157
$T_{1/2}$ (hrs)	4.28	4.39
$(AUC)_{0-12}^2$ (ng-hr/ml)	91.54	587.13
$(AUC)_{0-\infty}$ (ng-hr/ml)	114.20	708.13
K_a (hr^{-1})	0.4120	3.5526

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