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Pharmacokinetic Evaluation of Diclofenac Matrix Tablets Employing Cross Linked Starch-Urea

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ABSTRACT

Modified starches are promising and having good potential as release retardants and rate controlling polymers for controlled release. The controlled release properties of modified starches, generally based on solvent-activation have been intensively investigated. **Aim:** The present aimed to investigate the *in vivo* performance of the new polymer (Cross linked starch-urea or CLSU) in the formulation of controlled release dosage forms. **Methods:** Diclofenac matrix tablets employing CLSU were prepared by gelatinizing potato starch in the presence of urea and calcium chloride. 15 mg strength of diclofenac matrix tablets (B) were formulated employing CLSU and pure drug (A) were tested for *in vivo* pharmacokinetic evolution. Plasma drug concentration of Diclofenac was determined by HPLC method. 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_{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. **Results:** The absorption rate constant (K_a) was found to be $0.152h^{-1}$ for A and $0.817\ h^{-1}$ for B, and MRT was increased from 9.68 h for A to 14.05 h for B. T_{max} raised to 6 h for B from 3 h for A. Based on AUC_0^{α} the relative bioavailability of the diclofenac from CLSU was found to be 124.9% compared to diclofenac pure drug (100%). **Conclusion:** Thus the results indicated that starch urea cross-linked with calcium chloride is a promising matrix former for controlled release.

Keywords: Diclofenac, Matrix tablets, Cross-linked Starch-Urea, Controlled drug delivery.

INTRODUCTION

Controlled drug delivery is a topic of current interest in pharmaceutical technology and industry. In the last two decades, controlled release dosage forms have made significant progress in terms of clinical efficacy and potential compliance. Controlled release drug delivery systems are those formulations designed to release an active ingredient at rates, which differ significantly from their corresponding conventional dosage forms. The controlled release drug delivery systems are aimed at controlling the rate of drug delivery, sustaining the duration of therapeutic activity and / or targeting the delivery of the drug to a tissue. Drug release from these systems should be at a desired rate, predictable and reproducible.

A survey of the literature revealed that modified starches are promising and having good potential as release retardants and rate controlling polymers for controlled release. The controlled release properties of modified starches generally based on solvent-activation have been intensively investigated. For example, pre-gelatinized starch[1], cross linked amylose[2], substituted amylose[3], short-chained amylose (i.e. amylodextrin)[4,5] and calcium starch[6,7], all have retarded drug release from matrix tablets.

The formation of cross-linked starches with calcium salts is known in polymer chemistry. As the cross-linked polymers generally swell in water and aqueous fluids and form gelatinous matrices suitable for controlled release, it is thought worthwhile to investigate starch urea cross-linked with calcium chloride for its application in controlled release.

In the present investigation starch-urea cross-linked with calcium, a new modified starch polymer was synthesized and evaluated for its application in controlled release. Starch reacts with urea to form starch carbamate, a starch urea polymer. Khalil *et al.*[8] investigated the reactions between starch and urea resulting in the formation of starch – urea polymer. No reports are available on the pharmaceutical applications of starch urea. In the present study, starch urea cross–linked with calcium were evaluated for their applications in controlled release.

Diclofenac sodium known as diclofenac is a widely used non-steroidal anti-inflammatory analgesic and anti-pyretic drug. Controlled release formulation is needed for diclofenac because of its short biological half-life[9] of 2.0 h. The drug also causes[10] gastro intestinal disturbances, peptic ulceration with bleeding if present in large concentration in gastrointestinal tract. Hence, diclofenac is a suitable drug for oral sustained and controlled release and it would be advantageous to slow down its release in gastrointestinal tract not only to prolong its therapeutic action but also to minimize possible side effects of diclofenac.

MATERIALS AND METHODS

Diclofenac sodium is obtained as gift sample from M/s Micro Labs Ltd., Pondicherry, Methanol, Potassium dihydrogen phosphate, Sodium hydroxide, urea, Calcium chloride were procured from Qualigens fine chemicals Ltd. Potato starch was procured from Loba Chemie. Cross-linked starch urea (prepared in the laboratory) and all other chemicals used in the study were of analytical grade.

Animals

Healthy rabbits of either sex weighing 1.5-2.5 Kg were used in the study.

Preparation of Cross-linked starch urea polymer

Potato starch (9 parts) was dispersed in purified water (10 parts) to form starch slurry. Urea (1 part), calcium chloride (1 part) were dissolved in purified water (40 parts) and the solution was heated to boiling. While boiling, the starch slurry was added and mixed. Mixing while heating was continued for 20 minutes to form CLSU polymer. The mass formed was spread on to a stainless steel plate and dried at 85^0C for 6-8 h. The dried polymer was powdered and passed through mesh No. 120.

Preparation of matrix Tablets

Matrix tablets of 15mg diclofenac were prepared employing 50% CLSU. The drug and matrix material were mixed in mortar and the binder, water-alcohol (1:1) solution was added and mixed thoroughly to form dough mass. The mass was passed through mesh No.12 to obtain wet granules. The dried granules were passed through mesh No.24 to break aggregates. Passed granules were blended with talc 2% and magnesium stearate 2% in a closed polythene bag. The tablets granules were compressed in to tablets on rotary multi-station punching machine.

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 (pure drug and matrix tablets) were administered at a dose of 15 mg of diclofenac. After collecting the zero hour blood sample (blank), the products in the study was administered orally with 10 ml of water. Blood samples (2 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[11].

Plasma diclofenac concentrations estimated following the oral administration of diclofenac and its matrix tablets are given Table 1 and shown in Fig 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_{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[12,13].

Statistical Analysis

Data was analyzed by using one way ANOVA followed by Dunnett's t-test for multiple comparisons. Values with $P<0.05$ were considered significant[14].

RESULTS AND DISCUSSION

Pharmacokinetic evaluation was done on diclofenac matrix tablets (B) formulated employing CLSU in comparison to diclofenac pure drug (A) with a view to evaluate the release retarding and rate controlling efficiency of CLSU *in vivo*.

When the diclofenac matrix tablets formulated employing CLSU 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. 1) indicating slow absorption of diclofenac from the matrix tablets. A C_{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. 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 AUC_0^{α} the relative bioavailability of diclofenac from CLSU urea matrix tablets was found to be 124.9 % when compared to diclofenac pure drug (100 %).

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_{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. The results of the various pharmacokinetic parameters were given in Table 2.

CONCLUSION

The pharmacokinetic evaluation, thus, indicated that diclofenac from the matrix tablets formulated employing CLSU was released slowly and absorbed slowly over longer periods of time *in vivo* resulting in the maintenance of plasma concentrations within a narrow range over longer periods of time. As such CLSU exhibited good release retarding and rate controlling effect *in vivo* in the pharmacokinetic evaluation.

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Table 1. Plasma Concentrations of Diclofenac following the Oral Administration of Diclofenac (A) and Diclofenac matrix Tablets Formulated Employing Cross-linked Starch Urea (B) in rabbits (n = 6)

Time (h)	Plasma Concentration of Diclofenac $\bar{x}$ ± (s.d) (µg/ml)	
	A	B
0.5	1.5 ± (0.5)	0.8 ± (0.4)
1.0	2.3 ± (0.6)	1.0 ± (0.3)
2.0	4.1 ± (1.2)	1.9 ± (1.2)
3.0	4.7 ± (1.4)	2.2 ± (1.1)
4.0	4.5 ± (1.6)	2.6 ± (1.0)
5.0	4.3 ± (1.0)	2.8 ± (0.8)
6.0	4.0 ± (1.2)	2.9 ± (0.6)
8.0	3.1 ± (0.8)	2.8 ± (0.4)
10.0	2.8 ± (1.0)	2.8 ± (0.6)
12.0	2.7 ± (0.6)	2.7± (0.8)
16.0	1.5 ± (1.2)	2.5 ± (1.2)
20.0	0.8 ± (0.8)	2.3 ± (1.0)
24.0	0.6 ± (0.4)	1.9 ± (0.8)

Note: N=6. Values are statistically significant at $P<0.05$ (ANOVA)

Table 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)

Pharmacokinetic Parameter	A	B
C_{max} (µg/ml) ± (s.d)	4.7± (1.4)	2.9 ± (0.6)
T_{max} (h)	3.0	6.0
K_{el} (h^{-1})	0.1274	--
$t_{1/2}$ (h)	5.44	--
$(AUC)_0^{24}$ (µg.h/ml)	56.17	60.15
$(AUC)_0^{\alpha}$ (µg.h/ml)	60.10	75.06
K_a (h^{-1})	0.8172	0.152
MRT (h)	9.68	14.05
BA (%)	100	124.9

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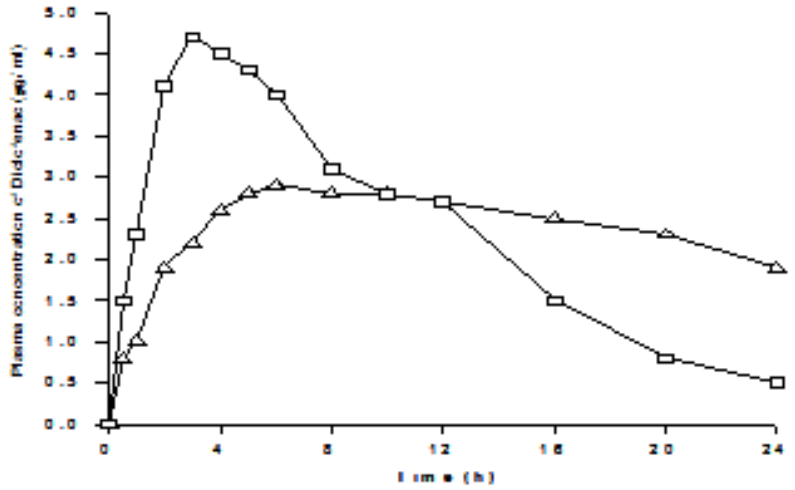

Figure 1. Plasma Concentration of Diclofenac Following the Oral Administration of Diclofenac (A) and Matrix Tablets Formulated Employing Cross-linked Starch Urea (B) in Rabbits (n=6)