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Research Article

RECLINICAL PHARMACOKINETIC EVALUATION OF PIOGLITAZONE FLOATING TABLETS FORMULATED EMPLOYING CROSS-LINKED STARCH-UREA

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ABSTRACT

The objective of the study is to make a pharmacokinetic evaluation of pioglitazone floating tablets formulated employing cross-linked starch urea in comparison to pioglitazone pure drug in rabbits. The two products were tested in a crossover RBD in healthy rabbits of either sex (n = 6). The plasma concentrations of pioglitazone were determined by a validated HPLC method. From the time versus plasma concentration data various pharmacokinetic parameters (Cmax, Tmax, $t_{1/2}$, AUC, Ka, MRT) were calculated. Pioglitazone from the floating tablets formulated was absorbed slowly over longer periods of time *in vivo* resulting in the maintenance of plasma concentrations within a narrow range over a longer period of time. The absorption rate constant (Ka) was decreased from 1.462 h^{-1} for pioglitazone pure drug to 0.225 h^{-1} with the floating tablets. MRT was increased from 9.82 h for pioglitazone pure drug to 13.48 h with the floating tablets. There was no increase in the bioavailability of pioglitazone form the floating tablets developed.

Keywords: Pioglitazone, Pharmacokinetics, Floating tablets, Cross linked starch urea.

INTRODUCTION

Pioglitazone is an effective oral anti - diabetic agent that belongs to the thiazolidone diones drug class and is widely prescribed in the management of non-insulin dependent (Type II) diabetes mellitus. It is poorly soluble in aqueous fluids and is majorly absorbed from stomach[1]. Dosage forms that are retained in the stomach would increase its oral bioavailability and efficacy. Pioglitazone has a short biological half-life of 3-6 hours and is eliminated rapidly[2]. Therefore sustained release floating tablet formulations are needed for pioglitazone to prolong its duration of action and to increase its oral bioavailability and to improve patient compliance. We reported earlier[3] the design of floating tablets of pioglitazone employing cross linked starch urea (a modified starch) as matrix former, sodium bicarbonate as gas generating agent, bees wax and ethyl cellulose as floating enhancers. These tablets exhibited a floating time of more than 44 hours after a floating lag time in the range 2 – 6 min and provided slow and complete release of pioglitazone over 24 hours.

In the present study pharmacokinetic evaluation was done on pioglitazone floating tablets formulated employing cross-linked starch urea as matrix former in comparison to pioglitazone pure drug in rabbits with a view to evaluate the *in vivo* performance of the floating tablets developed.

MATERIALS AND METHODS

Pioglitazone was a gift sample from M/s. Micro Labs, Ltd., Pondicherry. Cross-linked starch-urea (prepared in laboratory), Lactose (Qualigens), Sodium Bicarbonate (Loba Chemie), Talc I.P. (Loba Chemie), Magnesium stearate I.P. (Loba Chemie) were procured from commercial sources.

Preparation of cross-linked starch-urea polymer[4]

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 min to form cross-linked starch-urea polymer. The mass formed was spread on to a stainless steel plate and dried at 85 ^{0}C for 6-8 h. The dried polymer was powdered and passed through mesh No. 120.

Preparation of floating tablets for pharmacokinetic studies

Floating tablets (220 mg) each containing 10 mg of pioglitazone were prepared employing cross-linked starch-urea as matrix former at 50 % strength in the formulae and sodium bicarbonate (15%) as gas generating agent, bees wax (15 %) and ethyl cellulose (5 %) as floating enhancers. The tablets were prepared by wet granulation method. The required quantities of pioglitazone (sieve # 120), cross-linked starch-urea, bees wax, lactose (qs) were thoroughly mixed in a mortar by following geometric dilution technique. The granulating fluid (a mixture of water and alcohol in 1:1 ratio) was added and mixed thoroughly to form a dough mass. The mass was passed through mesh No. 12 to obtain wet granules. The wet granules were dried at 60 ^{o}C for 2 h. The dried granules were passed through mesh No. 16 to break the aggregates. The lubricants, talc (2 %) and magnesium stearate (2 %) were passed through mesh No. 60 on to the dry granules and blended in a closed polythene bag. The tablet granules were compressed into tablets on a 16 station rotary multi-station tablet punching machine (M/s Cadmach Machinery Co. pvt. Ltd., Mumbai) to a hardness of 8-10 kg/sq.cm using 9 mm round and flat punches.

Pharmacokinetic study

The following two products were tested for *in vivo* pharmacokinetic evaluation.

(i) Pioglitazone (10 mg) as a fine powder in hard gelatin capsule shells (Product A).

(ii) Pioglitazone (10 mg) floating tablets formulated employing cross-linked starch urea (Product B).

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 a validated HPLC method developed as follows.

The instrumentation of the HPLC system (Make: M/s Shimazdu Corporation, Japan.) consisted of UV-Visible detector (Shimadzu, Model: SPD – 10 AVP), C-18 column (Phenomenex, DESC: Gemini 5µ C18 110A, Size: 250 × 4.6 mm, S/No: 288063 – 23), 2 pumps (Model: LC – 10 ATVP) and a microsyringe of capacity 25 µm (Model: Microliter® # 702, Mfd. By: M/s Hamilton). The mobile phase was a mixture of acetonitrile – water (60:40) adjusted to pH 6.0 with 0.1 % v/v glacial acetic acid. The mobile phase was filtered through 0.45 µm membrane filter before use and was run at a flow rate of 1 ml/min. The column effluent was monitored at 269 nm.

For the estimation of pioglitazone in plasma samples, a calibration curve was constructed initially by analyzing plasma samples containing different amounts of pioglitazone. To 0.2 ml plasma in a dry test tube 1 ml of acetonitrile was added, mixed thoroughly and centrifuged at 5000 rpm for 20 min. The organic layer (0.5 ml) was taken into a dry tube and acetonitrile was evaporated. To the dried residue 0.5 ml of mobile phase (a mixture of acetonitrile – water (60:40) adjusted to pH 6.0 with 0.1% v/v glacial acetic acid) was added and mixed for reconstitution. Subsequently 20 µl were injected into the column for HPLC analysis.

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[5,6].

RESULTS AND DISCUSSION

Pharmacokinetic evaluation was done on pioglitazone floating tablets formulated employing cross-linked starch urea as matrix former in comparison to pioglitazone pure drug in rabbits with a view to evaluate the *in vivo* performance of the floating tablets developed. A summary of the pharmacokinetic parameters estimated following the oral administration of pioglitazone products tested is given in Table-1.

Table 1: Summary of Pharmacokinetic Parameters Estimated Following the Oral Administration of Pioglitazone (A) and its Floating Tablets formulated with cross linked starch urea (B) in Rabbits (n = 6)

Pharmacokinetic Parameter	A	B
C_{max} (µg/ml)	5.7±0.19	3.8±0.17
T_{max} (h)	3	6
K_{el} (h^{-1})	0.1199	--
$t_{1/2}$ (h)	5.78	--
$(AUC)_0^{24}$ (µg.h/ml)	78.92 86.60	68.15 80.12
$(AUC)_0^{\infty}$ (µg.h/ml)	1.462 9.82	0.225 13.48
K_a (h^{-1})	100	92.52
MRT (h)		
BA (%)		

The elimination rate constant (K_{el}) for pioglitazone was found to be 0.1199 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[7] 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 h^{-1}. A C_{max} of 5.7 ± 0.19 µg/ml was observed at 3.0 h after oral administration of pioglitazone pure drug. 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) indicating slow absorption of pioglitazone from the floating tablets. A C_{max} of 3.8 ± 0.17 µg/ml was observed at 6.0 h following the oral administration of floating tablets. The absorption rate constant (K_a) was found to be 0.225 h^{-1} with floating tablets (B). The plasma concentrations were stabilized and maintained within a narrow range for longer periods of time in the case of floating tablets (Fig. 1).

The mean residence time (MRT) was increased from 9.82 h for pioglitazone pure drug to 13.48 h with the floating tablets (B). The MRT value indicated longer stay of drug in the body when administered as floating tablets. Based on AUC_0^{∞} the relative bioavailability of pioglitazone from the floating tablets was found to be 92.52 % with floating tablets (B) when compared to pioglitazone pure drug (100 %).

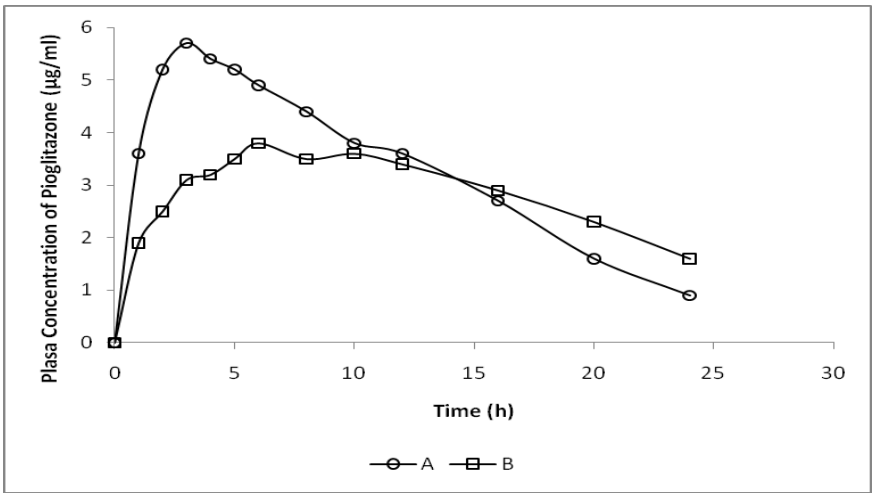

Fig. 1: Plasma Concentration of Pioglitazone Following the Oral Administration of Pioglitazone (A) and floating tablets with Cross-linked starch urea (B)

CONCLUSION

Pioglitazone from the floating tablets formulated was absorbed slowly over longer periods of time *in vivo* resulting in the maintenance of plasma concentrations within a narrow range over a longer period of time. The absorption rate constant (Ka) was decreased from 1.462 h^{-1} for pioglitazone pure drug to 0.225 h^{-1} with the floating tablets. MRT was increased from 9.82 h for pioglitazone pure drug to 13.48 h with the floating tablets. There was no increase in the bioavailability of pioglitazone form the floating tablets developed.

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