



PRECLINICAL PHARMACOKINETIC EVALUATION OF PIOGLITAZONE FLOATING TABLETS FORMULATED WITH SELECTED POLYMERS

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ABSTRACT

The objective of the present study is pharmacokinetic evaluation of pioglitazone floating tablets formulated employing olibanum, starch acetate 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.

The elimination rate constant (K_{el}) for pioglitazone was 0.1199 h^{-1} and the corresponding biological half life was 5.78 h following the oral administration of pioglitazone. 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 $5.7 \pm 0.19 \mu\text{g/ml}$ was observed at 3.0 h after oral administration of pioglitazone pure drug. Later the plasma concentrations were decreased rapidly. The absorption of pioglitazone was slow from all the three floating tablets formulated. The absorption rate constant (K_a) was found to be 0.133 h^{-1} , 0.225 h^{-1} and 0.1598 h^{-1} for floating tablets B, C and D respectively. The mean residence time (MRT) was increased from 9.82 h for pioglitazone pure drug (A) to 13.65 h, 13.48 h and 13.30 h respectively with the floating tablets B, C and D. Based on $AUC_{0-\infty}$ 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 %).

Keywords: Floating Tablets, Pioglitazone, Olibanum, Starch Acetate, HPMC K15M, Preclinical pharmacokinetics.

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 stomach¹. Dosage forms that are retained in the stomach would increase its oral bioavailability and efficacy. Pharmacological studies indicate that pioglitazone improves glycemic control while reducing circulating insulin level². Pioglitazone has short biological half-life of 3-6 hours and is eliminated rapidly.¹ Therefore controlled release (CR) products are needed for pioglitazone to prolong its duration of action and to improve patient compliance. Controlled release formulation is needed for pioglitazone for better control of blood glucose levels to prevent hypoglycemia and to enhance their

clinical efficacy and patient compliance.

Floating tablets of pioglitazone prepared employing (i) Olibanum (ii) starch acetate and (iii) HPMC K15M as rate controlling matrix formers at 50% strength, sodium bicarbonate (20%) as gas generating agent, bees wax (15%) and ethyl cellulose (5%) as floating enhancers exhibited excellent floating characteristics as well as controlled drug release over 24 h.

The objective of the present study is pharmacokinetic evaluation of pioglitazone floating tablets formulated employing olibanum, starch acetate 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.

EXPERIMENTAL

Materials:

Pioglitazone was a gift sample from M/s Micro

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labs Ltd., Pondicherry. Olibanum (Procured from Girijan Cooperative Corporation, Govt. of AP, Visakhapatnam.) Hydroxypropyl Methyl Cellulose (HPMC K 15M), Bees wax, Ethyl Cellulose (250 cps) and Sodium Bicarbonate were procured from commercial sources. Starch acetate was prepared in the laboratory as per a known method. All other materials used were of pharmacoeptial grade.

Methods:

Preparation of Floating Tablets

Matrix tablets each containing 30mg of pioglitazone was formulated employing (i) olibanum (ii) starch acetate and (iii) HPMC K15M. Sodium bicarbonate was used as gas generating agent at 20% strength in each case. The required quantities of pioglitazone, olibanum, starch acetate, HPMC K15M, lactose, sodium bicarbonate, ethyl cellulose and bees wax 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 dough mass. The mass was passed through mesh No. 12 to obtain wet granules. The wet granules were dried at 60°C for 2 h. The dried granules were passed through mesh No. 16 to break aggregates. The lubricants talc (2%) and magnesium stearate (2%) were passed through mesh No.100 on to dry granules and blended in a closed polyethylene bag. The tablet granules were compressed into tablets on a 16 station rotary multi- station tablet punching machine (Cadmach Machinery Co. Pvt. Ltd., Mumbai) to a hardness of 8-10 kg/sq.cm. using 9 mm round and flat punches.

Pharmacokinetic Evaluation:

The following products were tested for in *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 starch acetate (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 a known HPLC method³.

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 methods⁴⁻⁵.

RESULTS AND DISCUSSION

Pharmacokinetic evaluation was done on pioglitazone floating tablets formulating employing olibanum, starch acetate 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 polymers proposed for floating tablets. A summary of the pharmacokinetic parameters

estimated following the oral administration of pioglitazone products tested is given in Table 1. 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.

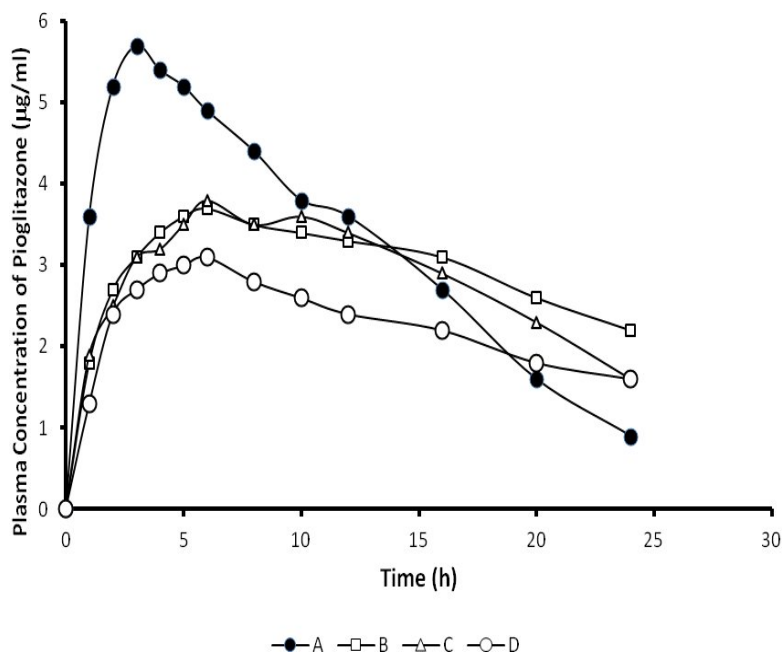


Fig. 1: Plasma Concentration of Pioglitazone Following the Oral Administration of Pioglitazone (A) and its Floating Tablets Formulated Employing Olibanum (B) starch acetate(C) and HPMC K15m (D)

Table 1: Summary of Pharmacokinetic Parameters Estimated Following the Oral Administration of Pioglitazone and its Floating Tablets in Rabbits (n = 6)

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

A: Pioglitazone; B: Floating Tablets with Olibanum; C: Floating Tablets with Starch acetate; D: Floating Tablets with HPMC K15M.

The $t_{1/2}$ value of pioglitazone obtained in the present work is in good agreement with the earlier reported¹ value of 3-6 h. The mean residence time (MRT) was found to be 9.82h. The absorption rate constant (K_a) was found to

be 1.462 h^{-1} . A C_{max} of $5.7 \pm 0.19\mu\text{g/ml}$ was observed at 3.0 h after oral administration of pioglitazone pure drug. A second peak concentration of $5.2 \pm 0.22\mu\text{g/ml}$ 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. 1) indicating slow absorption of pioglitazone from the floating tablets. A C_{max} of $3.7 \pm 0.12 \mu\text{g/ml}$, $3.8 \pm 0.17 \mu\text{g/ml}$ and $3.1 \pm 0.51 \mu\text{g/ml}$ 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 h^{-1} , 0.225 h^{-1} and 0.1598 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.1). The mean residence time (MRT) was increased from 9.82h 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 AUC_0^∞ 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 *in vivo* resulting in the maintenance of plasma concentration within a narrow range over a longer period of time.

CONCLUSIONS

1. The elimination rate constant (K_{el}) for pioglitazone was 0.1199 h^{-1} and the corresponding biological half life was 5.78

h following the oral administration of pioglitazone. 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 $5.7 \pm 0.19 \mu\text{g/ml}$ was observed at 3.0 h after oral administration of pioglitazone pure drug. Later the plasma concentrations were decreased rapidly.

2. The absorption of pioglitazone was slow from all the three floating tablets formulated. The absorption rate constant (K_a) was found to be 0.133 h^{-1} , 0.225 h^{-1} and 0.1598 h^{-1} for floating tablets B, C and D respectively.
3. The mean residence time (MRT) was increased from 9.82 h for pioglitazone pure drug (A) to 13.65 h, 13.48 h and 13.30 h respectively with the floating tablets B, C and D.
4. Based on AUC_0^∞ 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 %).

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