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A Factorial study on the formulation and evaluation of Pioglitazone controlled release Matrix Tablets

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Abstract: The objective of the present study was to formulate pioglitazone matrix tablets for controlled release. Controlled release matrix tablets of pioglitazone were developed for better control of blood glucose levels by prolonging its duration of action and to reduce GI disturbances with improved patient compliance. The tablets were prepared by wet granulation technique employing 50% w/w Hydroxypropyl methylcellulose K 15M as release controlling agent. Lactose and dicalcium phosphate were used as diluents. Polyvinyl pyrrolidone and polyethylene glycol 6000 were used as solubilizers. A 2^3 factorial design was applied for study and evaluation of the individual and combined effects of type of diluent (Factor A), polyvinyl pyrrolidone (Factor B) and polyethylene glycol 6000 (Factor C) on drug release from pioglitazone matrix tablets. Different dissolution models were applied to drug release data in order to evaluate release mechanisms and kinetics. All Pioglitazone matrix tablets followed first order kinetics, Higuchi drug release kinetics with diffusion as the dominant mechanism of drug release. As per Korsmeyer-Peppas equation, the release exponent 'n' ranged 0.663-0.892 indicating that drug release from all the batches was by non-Fickian diffusion mechanism. The type of diluent and solubilizers had highly significant effect on the drug release from the tablets ($P < 0.01$). The results of drug release study indicated that lactose as diluent gave relatively higher release rate than dicalcium phosphate. Polyethylene glycol 6000 gave relatively higher release than polyvinyl pyrrolidone. A combination of factors A, B and C gave slow, controlled and complete release of pioglitazone over a period of 24 hours.

Keywords: Piogliatzone matrix tablets, solubilizers, polyvinyl pyrrolidone, polyethylene glycol 6000, kinetic parameters.

INTRODUCTION:

Controlled-release systems are designed to enhance drug therapy. These systems are aimed to controlling the drug release rate and sustaining the duration of the action with or without targeted action. Oral controlled drug delivery system is the most popular, convenient and preferred method of administering therapeutic agents. One of the most common approaches used for controlling the rate of drug release is to incorporate the drug in rate controlling hydrophilic matrices. Drug release from these controlled systems should be at a desired rate and reproducible. The kinetics and mechanism of drug release from polymer matrices are dependent on the type and amount of polymer as well as on the physicochemical properties of the drug. [1]

Pioglitazone is an oral antidiabetic agent used in the management of noninsulin-dependent diabetes mellitus (NIDDM). It is selective agonist for peroxyzome proliferators-activated receptor-gamma (PPAR) and acts by activation of PPAR nuclear receptor, modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism. It decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output.[2,3] Pharmacological studies indicate that pioglitazone improves glycemic control while

reducing circulating insulin level. It has short biological half-life of 3-5 hours and eliminated rapidly. The drug also causes gastro intestinal disturbances such as gastric pain, constipation, nausea and vomiting if present in larger concentration in GI tract.[4] Therefore pioglitazone control release products are needed for better control of blood glucose levels by prolonging its duration of action and to reduce GI disturbances with improved patient compliance.[5,6]

Pioglitazone belongs to BCS class II and exhibits low solubility and dissolution rate characteristics, so it needs enhancement in solubility and dissolution rate for formulation in to controlled release matrix tablets. The purpose of the present investigation was to study and evaluate the individual and combined effect of type of diluents (DCP, Lactose) and solubilizers (PVP, PEG 6000) on drug release from pioglitazone matrix tablets formulated with HPMC K 15M employing 2^3- factorial study.

MATERIALS AND METHODS:

Materials: Pioglitazone hydrochloride and HPMC K 15M were kindly supplied by Dr. Reddy's Laboratories (Hyderabad, India). Lactose, Dicalcium phosphate (DCP), PEG 6000, Polyvinyl pyrrolidone (PVP) K30, Talc and Magnesium stearate were purchased from S. D. Fine Chemicals Ltd (Mumbai, India). All other ingredients were of analytical grade.

Experimental Factorial Design: The 2^3 factorial design was selected using three variables namely type of diluent (factor A), solubilizers PVP (factor B) and PEG 6000 (factor C) at two levels and factor levels were suitably coded. Eight formulations were prepared as per the design and coded (F_1-F_{abc}). The two solubilizers PVP K30 and PEG 6000 were selected and limits were chosen for detail studies using the factorial design. The amount of drug, HPMC K 15M, magnesium stearate, and talc were kept constant while diluent (Lactose / DCP) was taken in sufficient quantity to maintain a constant tablet weight of 220mg. The translation of the coded factor levels as percentage of ingredients is listed in Table 1.

Drug-excipient compatibility studies: To study the compatibility of HPMC K 15M with pioglitazone hydrochloride, solid admixture was prepared by mixing the drug with polymer in the ratio of 1:1 and stored in air tight container at 30±20˚C / 65±5% RH for three months. The solid admixture was characterized using Fourier transform infrared spectroscopy.

Preparation of standard curve of Pioglitazone Hydrochloride: 100 mg of pioglitazone hydrochloride pure drug was dissolved in 100 ml of 0.1 N HCl (stock solution-1000 µg/ml) and then placed in an sonicator for 10 min, from this 10 ml of solution was taken and then volume was adjusted to 100 ml with 0.1 N HCl (100 µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain the series of dilutions containing 2,4,6,8,10 µg/ml of pioglitazone hydrochloride solution. The absorbance of the above dilutions was measured at 269 nm by using the UV-Spectrophotometer using 0.1N HCl as the blank. Then a graph was plotted by taking concentration on X-axis and absorbance on Y-axis which gives a straight line.

Preparation and evaluation of Pioglitazone Matrix Tablets: Pioglitazone matrix tablets each containing 30 mg of API were prepared by wet granulation employing 50% w/w HPMC K 15M as release controlling polymer. The composition of eight formulations F_1-F_{abc} as per factorial design are shown in Table 2. The required quantities of

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drug, HPMC K 15M, PVP, PEG 6000 and diluents were weighed and mixed well. Then it was made into damp mass using a mixture of isopropyl alcohol and distilled water (1:1) as granulating fluid. The resulting damp masse was screened by passing them manually through sieve No. 12 and dried for 45 minutes at 60°C in the oven and then screened through sieve No. 16. The granules were mixed with the required quantities of lubricants and then compressed into tablets on a multi station rotary tablet compression machine using 9 mm round flat punches.

Characterisation of tablets [7]:

Tablet thickness: The thickness of ten (10) tablets was determined using a vernier calliper and the mean of these readings was taken as the mean tablet thickness.

Tablet weight uniformity: Ten (10) tablets were weighed individually on electric balance from which the mean was calculated and the percentage deviations were determined.

Crushing strength: The crushing strength of the three (3) tablets was determined individually with the Monsanto hardness tester and the mean crushing strength was calculated.

Friability: The friability of the tablets was determined using the Roche friabilator. Five (5) tablets were weighed and put into the friabilator and set to rotate at 25 rounds per minute for about four (4) minutes. The tablets were then removed and weighed again. The friability (F) is given by the formula; $F= (1-W/Wo)\times100$

Disintegration test: The prepared matrix tablets were subjected to disintegration test in distilled water, 0.1 N Hydrochloric acid and phosphate buffer of pH7.4.

Drug content: Ten (10) tablets were accurately weighed and powdered. From that powder, equivalent to 50 mg of pioglitazone was weighed and taken into boiling test tube and extracted with 40ml of methanol. The methanolic extract was collected into 50 ml of volumetric flask and the volume was made up to 50 ml with methanol. The solution was subsequently diluted with 0.1N hydrochloric acid and assayed for drug content by UV spectrophotometer at a wavelength of 269 nm.

Dissolution rate studies: Drug release studies from different formulated tablets were performed by using USP Type II apparatus in 900 ml of 0.1 N HCl as the dissolution medium, with a rpm of 50 and the bath was maintained at a temperature of 37 ± 0.5° C. Samples were withdrawn at regular intervals of time and these were replaced with equivalent volume of the fresh dissolution media. The withdrawn samples were analysed after suitable dilutions at a wavelength of 269 nm using UV spectrophotometer. The percentage drug release from the tablets was calculated from the absorbance values.

Kinetic treatment of dissolution data: Data obtained from in-vitro drug release studies were fitted to zero order ($Qt= Q0 + K0t$), first order ($\ln Qt = \ln Q_0 + K_1t$) kinetic equations. Higuchi [8] ($Qt =KHt^{1/2}$) and Korsmeyer-Peppas [9] ($Qt/Q\infty= Kt^n$) models were also applied to the dissolution data using linear regression analysis to know mechanism of drug release. A value of n=0.5 indicates case-I Fickian diffusion, 0.5<n<1 indicates anomalous non- Fickian diffusion, n=1 indicates case-II transport and n>1 indicates super case II transport.

RESULTS AND DISCUSSION

The major objective of the study was to design and evaluate pioglitazone matrix tablets for controlled release over a period of 24 hours. The individual and combined effect of type of diluent (Factor A), solubilizers PVP (Factor B) and PEG 6000 (Factor C) on drug release from pioglitazone matrix tablets formulated by employing HPMC K 15M were evaluated in a 2^3-Factorial study. Eight formulations of pioglitazone with selected combinations of diluents and solubilizers as per design were studied.

The Infrared spectra of pioglitazone hydrochloride solid admixture of drug and polymer was recorded between 500 to 3500cm-1 on FTIR. From the FTIR studies at 1693.6 and 1742.79 are the characteristics peaks of pioglitazone hydrochloride. No significant change occurred in the characteristic peaks of pioglitazone hydrochloride in the solid admixture. The spectrums shown in Figures 1,2.

The physical properties of the formulated matrix tablets were given in Table 3. Pioglitazone drug content of the tablets was within 100 ± 5% of the labeled content. Hardness was in the range 9-10.5 kg/sq.cm. Friability was less than 0.8% in all the cases. The prepared matrix tablets were found to be non-disintegrating in water, 0.1 N Hydrochloric acid and phosphate buffer of pH7.4. Hence all the pioglitazone matrix tablets formulated by employing HPMC K 15M and selected combinations of the three factors were of good quality and fulfilled the official specifications with regard to drug content, hardness and friability. Thus all the prepared matrix tablets were suitable for oral controlled release.

All the formulations of pioglitazone were subjected to in-vitro dissolution studies and corresponding results were shown in Figure 3. Drug release from the formulated matrix tablets was slow and spread over more than 24 hours. Analysis of the release data as per zero order and first order kinetic models. The correlation coefficient (r^2) values were higher in the case of first order kinetic model than in the case of zero order kinetic model indicating that the drug release from the formulated matrix tablets followed first order kinetics. Plots of percent release versus √time (Higuchi plots) were found to be linear with 'r^2' values >0.8804 in all the cases indicating diffusion as the release mechanism from all the matrix tablets. In the analysis of release data as per Korsmeyer-Peppas equation, the release exponent 'n' was in the range 0.6629-0.892 indicating non-fickian diffusion as the release mechanism from all the matrix tablets.

Drug release parameters of the matrix tablets were summarized in Table 4. Much variations were observed in the drug release characteristics of the matrix tablets. The release was dependent on the composition or factors involved in the formulation of matrix tablets. Drug release was only 68 – 71.23 % in 24 h in the case of formulations F1, Fa which were formulated employing lactose and DCP alone as diluents respectively. When the solubilizers, PVP and PEG 6000 were included in the matrix tablet formulations, the percent release was improved and the formulation Fabc gave 99.04 % release in 24 hours.

The significance of the individual and combined effects of the factors involved were tested by ANOVA of 2^3 – factorial design. The results indicated that the individual and combined effects of the three factors involved i.e. type of diluent (factor A), PVP (factor B) and PEG 6000 (factor C) were highly significant ($P < 0.01$). Thus

statistical analysis showed that the three factors significantly influences pioglitazone release from the matrix tablets.

The results of drug release study indicated that lactose as diluent gave relatively higher release than DCP. This is due to the hydrophilic and water soluble nature of lactose. PEG 6000 gave relatively higher release than PVP. A combination of factors, A, B and C (i.e. formulation, F_{abc}) gave slow, controlled and complete release of pioglitazone over 24 hours.

Conclusion:

The study was undertaken with the aim to evaluate the individual and combined effects of type of diluents (lactose / DCP) and solubilizers (PVP, PEG 6000) on drug release from pioglitazone matrix tablets formulated by employing HPMC K 15M as retarding agent .From the above results and discussion, it is concluded that pioglitazone controlled release matrix tablets formulated by employing HPMC K 15M as rate controlling polymer at 50% w/w strenght with DCP as diluent and solubilizers, PVP and PEG 6000 each at 2% strength, is considered as the best controlled release formulation of pioglitazone over a period of 24 hours i.e. for once a day administration.

Table 1: 2^3 Factorial design layout

Variable Levels	Factors		
	A (Type of diluent)	B (PVP)	C (PEG 6000)
I Level	Lactose	0%	0%
II Level	DCP	2%	2%

Table 2: Formulae of Pioglitazone Matrix Tablets Prepared as per 2^3 Factorial Design

Ingredients	Formulation composition (mg/tablet)							
	F1	Fa	Fb	Fc	Fab	Fac	Fbc	Fabc
Pioglitazone Hcl	30	30	30	30	30	30	30	30
Lactose	73	-	68.6	68.6	-	-	64.2	-
DCP	-	73	-	-	68.6	68.6	-	64.2
HPMC K 15 M (50% w/w)	110	110	110	110	110	110	110	110
PVP (2% w/w)	-	-	4.4		4.4		4.4	4.4
PEG 6000 (2%w/w)	-	-		4.4	-	4.4	4.4	4.4
Talc	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2
Total Weight	220	220	220	220	220	220	220	220

Table 3: Physical properties of pioglitazone controlled release matrix tablets

Physical parameter	Formulations							
	F1	Fa	Fb	Fc	Fab	Fac	Fbc	Fabc
Thickness (mm)	0.304±0.005	0.303±0.0	0.304±0.005	0.306±0.005	0.305±0.005	0.303±0.0	0.304±0.005	0.305±0.0
% weight variation	0.215±0.30	0.223±0.18	0.221±0.30	0.232±0.28	0.225±0.22	0.233±0.18	0.232±0.18	0.221±0.30
Drug content(%)	96.00	100.33	99.00	103.33	97.66	105.00	98.00	102.33
Friability (%)	0.7	0.6	0.8	0.5	0.6	0.4	0.7	0.8
Hardness (kg/Sq.cm)	10.5	10	9.5	9.5	10	9.5	10	9

Table 4: Drug release parameters of pioglitazone controlled release matrix tablets

Drug release parameter		Formulations							
		F1	Fa	Fb	Fc	Fab	Fac	Fbc	Fabc
Correlation coefficient (r^2)	Zero order	0.8733	0. 8804	0.9169	0.9416	0.9568	0.9589	0.9061	0.8774
	First order	0.9889	0.9757	0.9778	0.9491	0.9776	0.9692	0.9875	0.8724
	Higuchi's	0.9485	0.8804	0.9316	0.9084	0.9018	0.8975	0.9427	0.9497
$K_1 \times 10^{-2}$ (hr^{-1})		4.97	4.41	5.98	7.37	4.91	5.95	6.27	9.82
n-value (Korsmeyer-Peppas)		0.679	0.892	0.663	0.733	0.743	0.732	0.706	0.669
T_{50} (hr)		13.94	15.71	11.59	9.40	14.11	11.65	11.05	7.05
T_{90} (hr)		46.34	52.22	38.51	31.25	46.9	38.71	36.73	23.45
% Drug released at 24hr		71.23	68.32	80.41	89.54	75.59	80.23	80.95	99.04

Figure 1: FTIR spectra of pure Pioglitazone hydrochloride

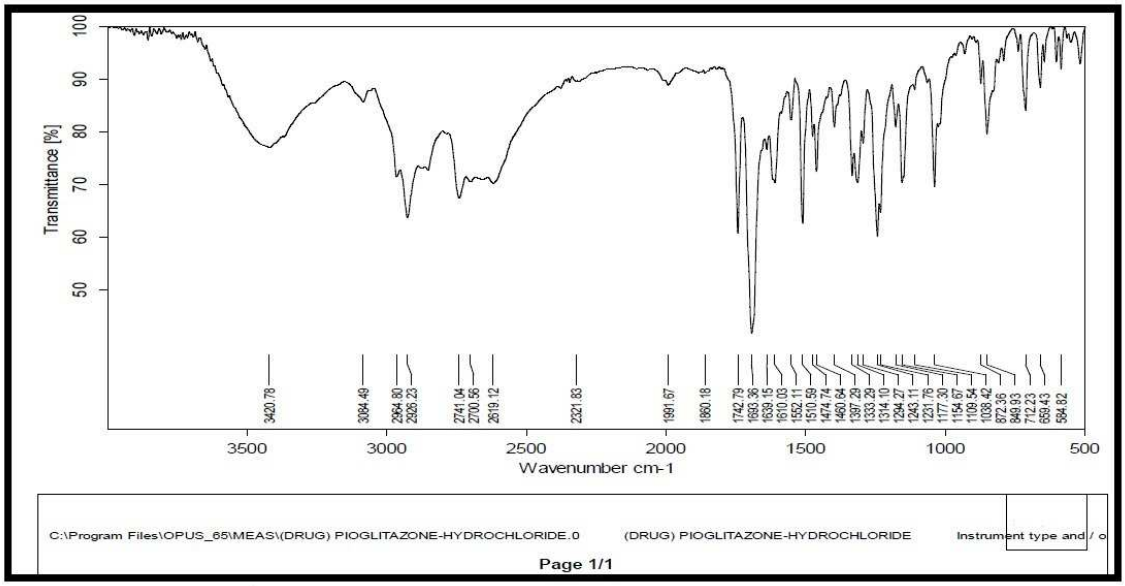


Figure 2: FTIR spectra of physical mixture of Pioglitazone hydrochloride with HPMC K15M

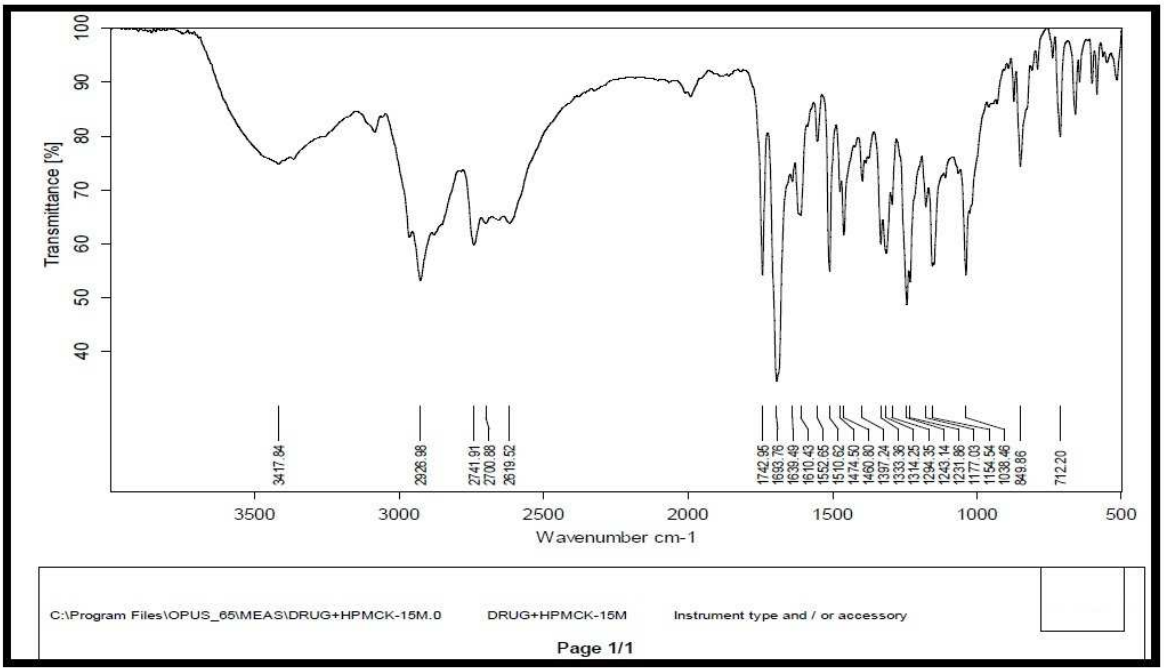
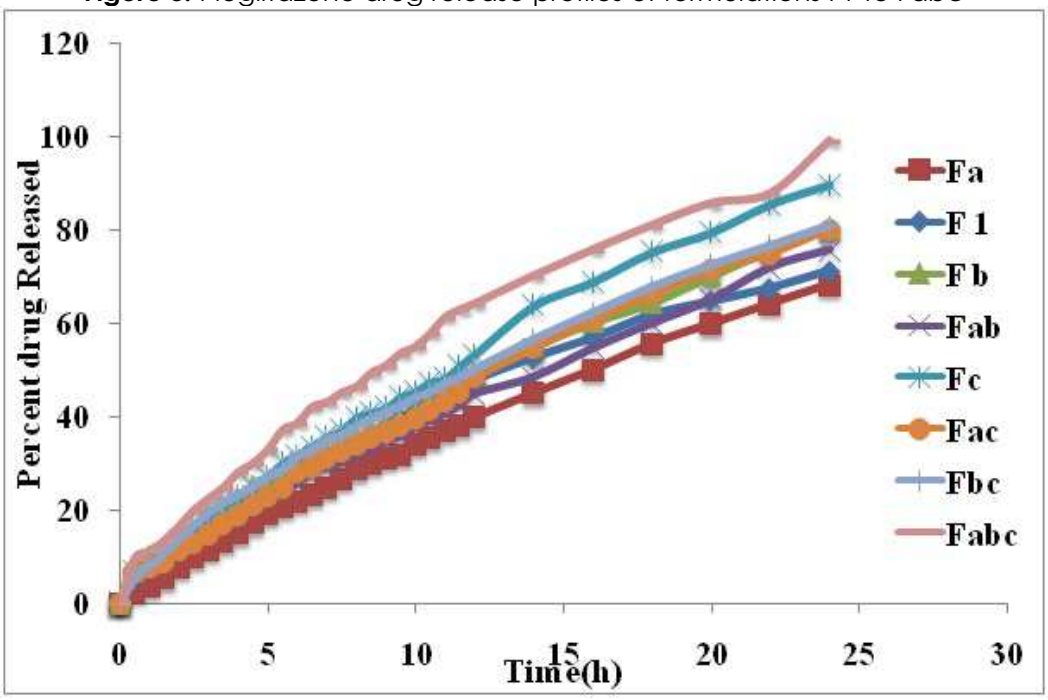


Figure 3: Pioglitazone drug release profiles of formulations F1 to Fabc



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