Research Article

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Formulation and evaluation of pioglitazone sustained release matrix tablets

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ABSTRACT

The aim of the present work is to Formulate and Evaluate sustained release of Pioglitazone matrix tablets used for treatment of diabetes mellitus. Development of SR Pioglitazone is proposed considering the adverse event profile and high fluctuation index of Pioglitazone observed with SR dosage forms. In the present work, attempts were made to formulate and evaluate sustained release of matrix tablets of Pioglitazone. Pioglitazone was subjected to preformulation studies, based on the results obtained Pioglitazone sustained release tablets were successfully formulated. Formulations prepared by direct compression technique using various polymers. Set of trials were formulated for which Pioglitazone evaluated parameters (bulk density, tapped density, compressibility index, hausner's ratio, weight, thickness, hardness) were found to lie within the specifications. Dissolution study was performed in USP type II apparatus at 100 RPM in pH 6. 8 phosphate buffer. From the results of the invitro study it appears that the release of the Pioglitazone was significantly influenced by the characteristics of the polymer used.

Keywords: Pioglitazone, Polymers, Direct compression technique, FTIR studies, In Vitro drug release studies.

INTRODUCTION

Oral drug administration has been the predominant route for drug delivery. Sustained release dosage forms have been demonstrated to improve therapeutic efficiency by maintenance of a steady drug plasma concentration. Sustained release, prolonged release, modified release, extended release or depot formulations are terms used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. [1, 2] Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. Matrix tablet is one of the most widely used approaches to sustain the drug action. [2] Matrix tablets may be defined as the "oral solid dosage forms in which the drug or active ingredient is homogeneously dispersed throughout the hydrophilic or hydrophobic matrices which serves as release rate retardants". Matrix drug delivery systems release the drug in continuous manner. These release the drug by both dissolution controlled as well as diffusion controlled mechanisms. [3, 4] Pioglitazone is an oral antidiabetic agent used in the management of noninsulin dependent diabetes

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mellitus (NIDDM). 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. [5]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. [6]

MATERIALS AND METHODS

Pioglitazone was collected as a gift sample from Hetero labs, Hyderabad and various excipients like Eudragit, ethylcellulose and hydroxyl propyl methyl ellulose were purchased from AR chemicals, Hyderabad.

METHODOLOGY [7, 8]

Compatibility studies of drug and polymers

In the formulation of Pioglitazone tablet formation, API and Excipient may interact as they are in close communication with each other, which could lead to the instability of drug. FT-IR spectroscopy was employed to ascertain the compatibility between Pioglitazone and the selected polymers. The pure drug and drug with excipients were scanned separately.

Formulation Development

Table-: Formulation of Pioglitazone tablets

S.NO.	INGREDIENTS	F1	F2	F3	F4
1	Pioglitazone	10	10	10	10
2	HPMCk4M	100	-	-	50
3	Ethylcellulose	-	100	-	50
4	Eudragit	-	-	100	-
5	Microcrystalline Cellulose	85	85	85	85
6	Magnesium stearate	3	3	3	3
7	Talc	2	2	2	2
8	Total Wt	200	200	200	200

Preparation technique [9, 10]

Direct compression method

Sustainedreleasetablets of pioglitazonewere prepared by direct compression. All the ingredients were passed through 60#mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 100mg using 8 mm round flat punches on 10 station rotary tablet machine (Rimek).

EVALUATION STUDIES [11, 12]

Bulk Density

Bulk density is defined as the mass of powder divided by bulk volume.
It is calculated using the following equation:
Bulk density = weight of sample taken /volume noted

Tap density

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (v_o) was measured.
Tapped density = weight of sample taken / tapped volume
Where,
V_o = initial volume
V_f = final volume.

Compressibility index

Based on the apparent bulk density and the tapped density, the percentage Compressibility of the bulk drug was determined by the following formula.
Carr's index = Tapped density - Bulk density / Tapped density X 100

Hausner's ratio

It indicates the flow properties of the powder. The ratio of tapped density to the bulk density of the powder is called Hausner ratio.

Hausner's ratio = Tapped density / Bulk density

Angle of repose

The flow characteristics are measured by angle of repose. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

$\tan\theta = h/r$

Where

h = height of pile

r = radius of the base of the pile

= angle of repose

Evaluation of tablet [13-15]

Weight variation

Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more then two of the individual tablet weight deviate from the average weight by more than the percentage.

Thickness

Twenty tablets were randomly selected form each batch and there thickness was measured by using vernier caliper. Thickness of three tablets from each batch was measured and mean was calculated.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets were determined.

Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Twenty tablets were weighed and placed in the Roche friabilator, which was then operated for 25 rpm for 4 min. After revolution Tablets were dedusted and reweighed. Compressed tablets should not loose more than 1% of their weight.

The percentage friability was measured using the formula,

$\% F = \{1-(Wo/W)\} \times 100$

Where,

% F = friability in percentage

Wo = Initial weight of tablet

W = weight of tablets after revolution

Content Uniformity

Twenty tablets from each batch were powdered and weighed accurately equivalent to 100 mg Pioglitazone. Dissolve the weighed quantity of powder into 100 ml of 6.8 phosphate buffer solution by stirring it for 15 min. 1 ml of solution was pipette out into 10 ml volumetric flask, to it 10 ml of 6.8 phosphate buffer solution was added. Immediately analyze the drug by taking absorbance.

In- Vitro Release study

In-Vitro drug release studies were carried out using Tablet dissolution test apparatus USP II at 100 rpm. The dissolution medium consisted of 900 ml of Standard buffer pH pH 6.8 for 8 hrs. Temperature maintained at 37±1. The sample of 5ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. From that 5 ml sample, 1 ml sample was withdrawn and placed in a 10 ml volumetric flask, to it add 10 ml 6.8 phosphate buffer solution. Immediately analyze the drug by taking absorbance.

Stability studies

The success of an effective formulation can be evaluated only through stability studies. The prepared Matrix tablets of Pioglitazone were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, $40\pm2^{o}c$ and refrigerator $2\text{-}8^{o}c$ for a period of 30 days.

RESULTS & DISCUSSION

FTIR Studies

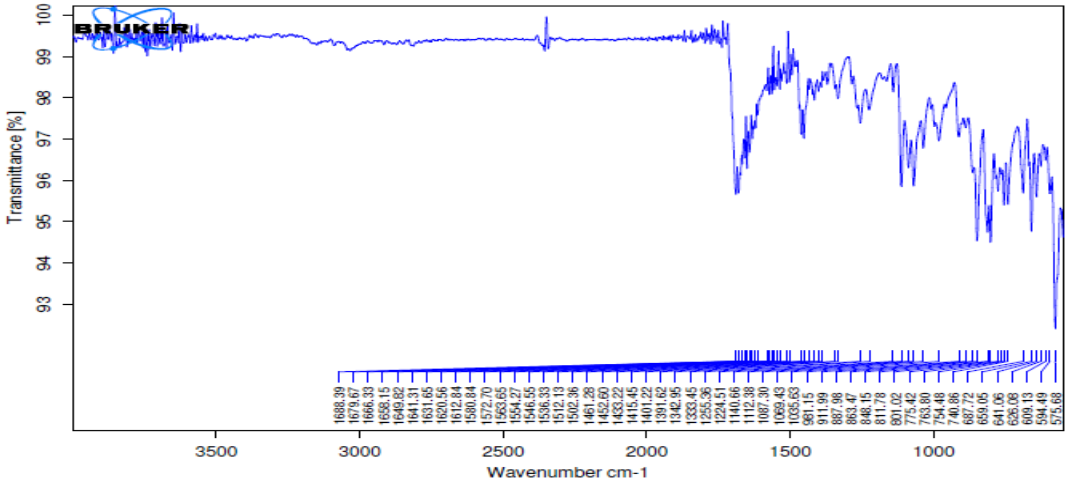

Fig-: FTIR Studies of Pure drug

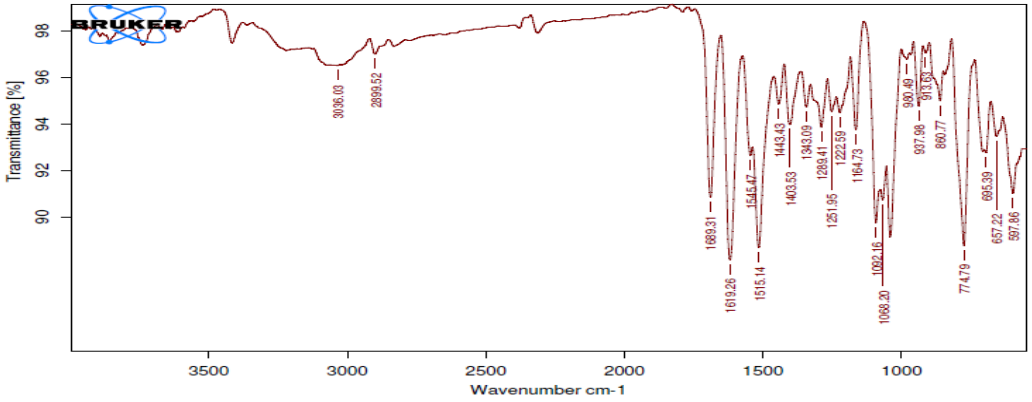

Fig-: FTIR spectra Optimised formula

EVALUATION STUDIES

Pre compression parameters

Bulk Density

The bulk density for the formulated blend was carried out for all formulation and found in the range of 0.399-0.412.

Tapped density

The tapped density for the formulated blend was carried out for all formulation and found in the range of 0.525-0.546.

Angle of repose

The angle of repose for the formulated blend was carried out. It concludes that all the formulations blend was found to be in the range of 28^0 to 31^0

Compressibility index

Compressibility index was carried out, it found between 10% to 24.54 % indicating the powder blend have the required flow property for compression.

Table-: Results for pre compression parameters

F. no	Bulk density	Tapped density	Compressibility index	Hausner ratio	Angle of repose(0)
F1	0.412	0.546	24.54	1.32	29^0
F2	0.399	0.531	24.85	1.33	30^0
F3	0.410	0.541	24.21	1.31	28^0
F4	0.400	0.525	23.80	1.31	31^0

Post compression parameters

Weight variation

All the formulated (F1 to F4) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness

Tablets mean thickness were uniform in F1 to F4 formulations and were found to be in the range of 3.28 mm to 3.35mm.

Hardness

The measured hardness of tablets of each batch ranged between 4.16 to 4.63 kg/cm^2 .This ensures good handling characteristics of all batches.

Friability

The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity

The percentage of drug content for F1 to F4 was found to be between 90.58% and 93.55 % of Pioglitazone, it complies with official specifications.

Table-: Physical parameters of tablets of each batch

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	200	3.35	4.25	0.43	90.58
F2	200	3.29	4.32	0.51	93.55
F3	199	3.31	4.63	0.43	91.42
F4	200	3.28	4.51	0.50	90.55

In-vitro Dissolution Study

All the eight formulation of prepared matrix tablets of Pioglitazone were subjected to in-vitro release studies these studies were carried out using dissolution apparatus. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for the 8 hrs.

Table-: Dissolution Profile of F1 to F8

Time (hrs.)	F_1	F_2	F_3	F_4
0	0	0	0	0
1	21.39	25.96	23.36	20.32
2	36.42	38.15	35.96	30.18
3	41.26	45.96	40.88	39.89
4	52.58	58.91	51.28	51.18
5	63.98	68.78	62.15	63.25
6	71.26	75.84	70.25	75.68
7	80.56	86.93	81.56	84.59
8	91.65	96.18	90.25	91.56

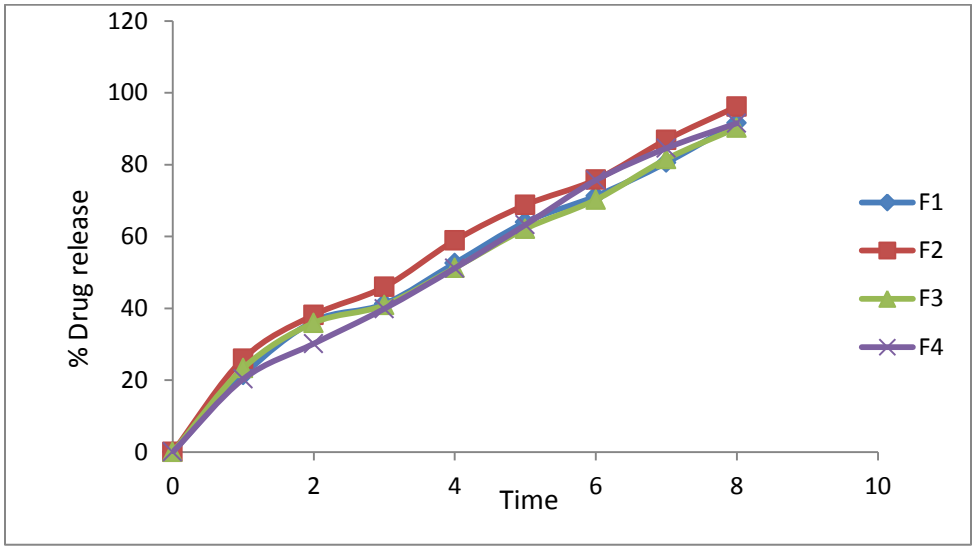

Fig-: Dissolution profile of all Formulations

Stability studies

Sustained release matrix tablets of Pioglitazone formulated in the present study were subjected to accelerated stability studies. Stability studies of the prepared formulations were performed at ambient humidity conditions, at room temperature, at 40°c and 2-8°c for a period up to 30 days. The samples were withdrawn after periods of 90 days and were analyzed for its appearance, hardness, friability, drug content and in vitro release. The results revealed that no significant changes in appearance, drug content, hardness, friability, and in vitro release for F2 formulation. When it was stored at the three storage conditions. However there was slight variation in in vitro release when it is stored at 2-8°c, there was no change when it is stored at 40°c and room temperature.

Table-: Results of stability studies of optimized formulation F-2

Formulation Code	Parameters	Initial	1st Month	Limits as per Specifications
F-2	25°C/60%RH	96.18	96.15	Not less than
	% Release			85 %
F-2	30°C/75% RH	96.18	96.12	Not less than
	% Release			85 %
F-2	40°C/75% RH	96.18	96.09	Not less than
	% Release			85 %

CONCLUSION

The present study was undertaken with an aim to formulate and evaluate Pioglitazone sustained release tablets using different polymers as release retarding agents. Preformulation study was carried out and all the parameters were found within the specification. Hence different batches of Pioglitazone were prepared using selected excipients. Powders were evaluated for Bulk density, tapped density, compressibility index, Hausner ratio before being punched as tablets. Various formulations of sustained release tablets of Pioglitazone were prepared by using different polymers in different proportions by Direct compression technique. The tablets were evaluated for physical parameters, *in vitro* release study and stability studies. In-vitro release indicated that the formulation F2 had better dissolution profile along with sustained action as compare to other formulations. Stability study was conducted on tablets of Batch F2 stored at room temperature, 40°C, and 2-8°C for one month. Tablets were evaluated for hardness, friability, in-vitro release profile and drug content. No significant changes were observed in any of the studied parameters

during the study period (30days), thus it could be concluded that formulation was stable. From the results it can be concluded that sustained release tablet of Pioglitazone containing ethylcellulose i.e. F2 can be formulated successfully.

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