WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 8, 2891-2912. Research Article ISSN 2277– 7105

FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF PIOGLITAZONE

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Article Received on
19 June 2015,

Revised on 10 July 2015,
Accepted on 05 Aug 2015

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ABSTRACT

Pioglitazone Hydrochloride is an oral anti-diabetic agent, which acts primarily by increasing insulin dependent glucose disposal. There is a need for sustained release Pioglitazone formulations, which overcome the various problems associated with the use of this drug in the prevention and treatment of diabetes. The floating tablets were prepared by wet granulation method. In the present work efforts have been made to develop floating drug delivery system for Pioglitazone Hydrochloride with hydrophilic and hydrophobic polymer in different ratios to achieve a sustained release for 24 hrs. The in vitro drug release profile of Pioglitazone hydrochloride tablets containing Ethyl Cellulose, Xanthan gum and Eudragit RS100 gave desired drug release profile. The tablets of all formulation were subjected to various physicochemical evaluation parameters such as thickness, diameter, weight variation, hardness, friability, drug content, in-vitro buoyancy lag time, total floating time, tablets density, swelling index and in-vitro dissolution study. The results of all these tests were found to be satisfactory within the prescribed limits. The formulations showed higher R^2 values for zero order plots indicating that drug release followed zero order kinetics.

KEYWORDS: Pioglitazone hydrochloride, Ethyl Cellulose, sustained release matrix tablets.

INTRODUCTION

Enteral route is the most oldest and convenient route for the administration of therapeutic agents because of low cost of therapy and ease of administration leads to higher level of patient compliance. Approximately 50% of the drug products available in the market are administered orally and historically, oral drug administration has been the predominant route for drug delivery. Tablets are the most commonly and widely used dosage form. This type of drug delivery system is called conventional drug delivery system and is known to provide an immediate release of drug. Such immediate release (IR) products results in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. However, after absorption of drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetics profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached another dose is usually given if a sustained therapeutic effect is desired. Conventional formulations are required to be administered in multiple doses and therefore have several disadvantages.[1]

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. The goal in designing sustained delivery system is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, sustained release dosage form is a dosage form that release one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ. Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. Various approaches are used to Sustained Release Drug Delivery System. These are: Diffusion sustained systems, Dissolution sustained systems, Dissolution and diffusion sustained systems, Ion exchange resin- drug complexes, pH dependent formulation, Osmotic pressure controlled systems, Swelling and expansion systems, Floating systems and Bioadhesive or Mucoadhesive systems. Matrix tablet is one of the most widely used approach to sustained the drug action. 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.[2] Pioglitazone belongs to BCS class-II and a member of the thiazolidinedione class (TZD) with hypoglycemic action. Pioglitazone selectively stimulates the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ) and to a lesser extent PPAR-α.Pioglitazone is used for the treatment of diabetes mellitus type 2 in monotherapy and in combination with a sulfonylurea, metformin, or insulin. Pioglitazone has also been used to treat non-alcoholic steatohepatitis, but this use is presently considered experimental. Pioglitazone has also been found to reduce the risk of conversion from prediabetes to diabetes mellitus type 2 by 72%. Pioglitazone also lowers the level of glucose in the blood by reducing the production and secretion of glucose into the blood by the liver.[3] Pioglitazone hydrochloride has short half life (3- 7 hrs).To reduce the frequency of administration and to improve patient compliance, sustained release formulation is desirable. The most commonly method of modulating the drug release is to include it in a matrix system. Because of their flexibility, hydrophilic polymer matrix systems are widely used in oral controlled drug delivery to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance.[4, 5] Hence in the present work an attempt has been made to develop sustained release matrix tablets of Pioglitazone using hydrophilic and hydrophobic matrix materials like xanthan gum, ethyl cellulose, eudragit RS 100 etc. Several sustained release formulation have been prepared for Pioglitazone by different polymers and techniques.

MATERIALS

Pioglitazone hydrochloride was obtained as a gift sample from Ananta Medicare Ltd., Sri Ganganagar (Raj). Xanthan gum, Eudragit RS 100, Ethyl cellulose, Carbopol 974 etc. All excipients were of laboratory reagent grade.

METHODS

Drug Identification (λ_{max}) [6]

- **By absorption spectrum method**

Accurately weighed 1mg of Pioglitazone and dissolved in 10ml 0.1N HCl (100µg/ml). 2.5 ml solution was taken and diluted up to 10 ml (25µg/ml). This solution was scanned between 200-400nm. The maximum obtained in the graph was considered as λ_{max} for the pure drug.

- **By infra-red spectra method**

Accurately weighed 10mg of Pioglitazone and polymers taken in vials and scanned in FTIR immediate and after 15 days (kept at 50°C) for drug polymer identification.

Drug Excipient Compatibility Studies by FTIR

Drug and different excipients were taken in 1:1 ratio. The excipients used xanthan gum, ethyl cellulose, carbopol 974 and Eudragit RS- 100. Drug and excipients were accurately weighed and mixed and the resulting mixtures were scaled in screw glass vials and kept at 50°C for 15 days . Observations of samples were taken for observing change in their appearance, colour and odour. These studies performed from faculty of pharmaceutical sciences Jodhpur National University. The samples of pure drug and physical mixture of polymer and drug were taken and subjected to FTIR study.[7]

Standard Calibration Curve of Pioglitazone in 0.1N HCl

100mg of Pioglitazone was accurately weighed and dissolved in 100ml 0.1N HCl to give a solution of 1000 µg/ml concentrations and this served as the first standard stock solution. From this stock solution 10 ml was taken and diluted to 100 ml using buffer to get a solution of 100 µg/ml concentrations and this solution served as the second standard stock solution. From this second stock solution, the solution containing concentration of (i.e.) 0.5 ml (5µg/ml), 1 ml (10 µg/ml), 2 ml (20 µg/ml), 3 ml (30 µg/ml), 4 ml (40 µg/ml), 5 ml (50 µg/ml) were prepared. Absorbances of these solutions were measured at the obtained λ_{max} using UV- Visible Spectrophotometer and standard graph was plotted.[6]

Formulation of Floating Tablet

The required quantities of Pioglitazone, sodium alginate, ethyl cellulose, xanthan gum, eudragit RS 100, carbopol 974 were thoroughly mixed in a mortar by following geometric dilution technique. The granulating fluid (a mixture of starch paste) 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^{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 to a hardness of 8-10 Kg/cm^2 using 8 mm round and flat punches.[8]

Evaluation parameters

Percentage Practical Yield

Thoroughly dried granules were collected and weighed accurately. The percentage practical yield was calculated using formula given below,

$$\text{Percentage Practical Yield} = \frac{\text{Mass of granules obtained}}{\text{Total weight of drug, polymer \& excipients}} \times 100$$

Determination of drug content

Twenty tablets were weighed and powdered the powder weight equivalent to 100mg of Pioglitazone was dissolved in 100ml of 0.1N HCl and filtered. 5ml of this was diluted to 50ml with 0.1N HCl and drug contents were estimated with UV-Visible spectrophotometer at 269nm.

$$\text{Drug content (\%)} = \frac{G_{act}}{G_{powder}} \times 100$$

In vitro dissolution test

Drug release from the matrix tablets was studied using 8-station dissolution rate test apparatus (Lab India, Disso 2000) employing a paddle stirrer at 50 rpm and at temperature 37 ± 0.5°C. Hydrochloric acid, 0.1 N (900 ml) was used as dissolution fluid. A 5 mL sample of dissolution fluid was withdrawn at different time intervals through a filter (0.45µm) over a period of 24h. Each sample withdrawn was replaced with an equal amount of fresh dissolution medium. The samples withdrawn were assayed spectrophotometrically by measuring the absorbance at 269 nm.[9]

Pre-compression parameters[10]

Micromeritic evaluation

Prior to the compression, the formulation granules were evaluated for their bulk and tapped density and from these values compressibility index and Hausner's ratio were calculated. While the flow properties of the granules were accessed from the angle of repose.

Bulk density

The bulk density of the formulated granules was evaluated using a bulk density apparatus. It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a graduated measuring cylinder and the volume was noted. It was expressed in gm/ml and is given by

$$\text{Bulk Density } (\rho_b) = \frac{\text{Mass of the powder (M)}}{\text{Volume of the bulk powder } (V_b)}$$

Tapped density

It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It was expressed in gram/ml and is given by

$$\text{Tapped Density } (\rho_t) = \frac{\text{Mass of the powder (M)}}{\text{Tapped Volume of the powder } (V_t)}$$

Compressibility Index and Hausner Ratio

The Compressibility index and Hausner's ratio are measures of the propensity of a powder to be compressed and the flow ability of granule. As such, they are measures of the relative importance of inter-particulate interactions. Carr's index and Hausner's ratio were calculated using following formula

$$\text{Carr's Index (I)} = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

Where, ρ_t – Tapped density of the powder

ρ_b – Bulk density of the powder

$$\text{Hausner's ratio} = \frac{\rho_t}{\rho_b}$$

Table 1: Range of compressibility index and Hausner ratio

Compressibility index (%)	Flow character	Hausner ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very, very poor	>1.60

Angle of repose

The frictional forces in a loose powder can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane. Sufficient quantities of Pioglitazone granules were passed through a funnel from a particular height onto a flat surface until it formed a pile, which touched the tip of the funnel. The height and radius of the pile were measured. The angle of repose was calculated using the formula

Tan θ = h/r

$\theta = \tan^{-1}$ (h/r)

Where, θ is the angle of repose, h = height of pile, r = radius of the pile base

Table 2: Range of angle of repose

Flow Property	Angle of Repose (Degrees)
Excellent	25-30
Good	31-35
Fair-aid not needed	36-40
Passable-may hang up	41-45
Poor-must agitate, vibrate	46-55
Very poor	56-65
Very, very poor	>66

Post compression parameters [11]

Shape of Tablets

Compressed tablets were examined under the magnifying lens for the shape of the tablets.

Tablet Dimensions

Thickness and diameter of tablets were measured using Vernier Callipers. It was determined by checking ten tablets from formulation. It was expressed in mm.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Pfizer hardness tester. It was expressed in kg/cm^2. Ten tablets were selected and hardness of the tablets was measured.

Friability

For tablets with an average weight of 0.65 g or less take a sample of whole tablets corresponding to about 6.5 g and for tablets with an average weight of more than 0.65 gtake a sample of 10 whole tablets. Dedust the tablets carefully and weigh accurately the required number of tablets. Place the tablets in the Roche friabilator. The friabilator was operated at 25 rpm for 4 minutes (100 revolutions) then remove any loose dust from them and weigh them accurately. A maximum loss of weight not greater than 1.0 per cent was acceptable for most tablets .The percent friability was calculated using equation. [12]

$$\% F = 1 - \frac{W_o}{W} \times 100$$

Where, % F = friability in percentage

W = Initial weight of tablet

W_0 = weight of tablets after revolution

Weight variation test

Weigh individually 20 units selected at randomly and calculate the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage and none deviates by more than twice that percentage as shown in Table 3.

Table 3: Weight variation ranges as per I.P.

Average weight	Percentage deviation
80 mg or less	10
More than 80 mg but less than 250 mg	7.5
250 mg or more	5

In vitro buoyancy studies

The test for buoyancy was usually performed in USP dissolution apparatus containing 900ml 0.1 N HCl at 37^0 C as the testing medium. The time required for the tablet to rise to the surface and float was determined as Floating Lag Time (FLT) and the time period up to which the tablet remained buoyant is determined as Total Floating Time (TFT).

Swelling index

The floating tablets were weighed individually (designated as W0) and placed separately in glass beaker containing 200 ml of 0.1 N HCl and incubated at 37°C±1°C. At regular 1h time intervals until 24h, the floating tablets were removed from beaker and excess surface liquid was removed carefully using the tissue paper. The swollen floating tablets were then re-weighed (Wt), and % swelling index was calculated using the following formula.[12, 13]

Swelling Index (%)= $\frac{W_t - W_0}{W_0} \times 100$

Dissolution of final formulation

In vitro dissolution study was carried out for optimized formulation of floating tablet in 0.1N HCl and analyzed at 269 nm by UV spectrophotometer and plotted graph.

Release kinetics

Release kinetic models, which described the overall release of drug from the dosage forms. Because qualitative and quantitative changes in a formulation may alter drug release and in vivo performance, developing tools that facilitate product development by reducing the necessity of bio-studies is always desirable. In this regard, the use of in vitro drug dissolution data to predict in vivo bio-performance can be considered as the rational development of controlled release formulations. Data obtained from the in vitro release studies were fitted to various model dependent kinetic equations such as zero order, first order, Higuchi model and Korsmeyer- Peppas model.[14]

Zero-order model

$Q_t = Q_0 + K_0 t$

First order model

Log C= log C_0- Kt/2.303

Higuchi model

Q= $K_H \times t^{1/2}$

Korsmeyer-Peppas model

$Q/Q_0 = Kt^n$

Where, K_0 to K_H were release rate constants, Q/Q_0 was fraction of drug released at time t, K was a constant and n was diffusion constant that indicates general operating release mechanism. For Fickian (diffusion controlled), $n \leq 0.5$; for non- Fickian (anomalous) release, 'n' value is in between 0.5 to 1.0; for zero order release, n=1.0; for super case transport II, $n > 1.040$. Based on the slope and the R^2 values obtained from the above models the mechanism of drug release was determined.

RESULTS AND DISCUSSIONS

PREFORMULATION STUDIES

Drug Identification (λ_{max})

- **By absorption spectrum method**

The accurately weighed quantity of drug was dissolved in sufficient volume of 0.1N HCl and scan was obtained on UV-VIS spectrophotometer. The wavelength at which maximum absorbance obtained was considered as maximum wavelength (λ_{max}) i.e 269.4 nm for the drug.

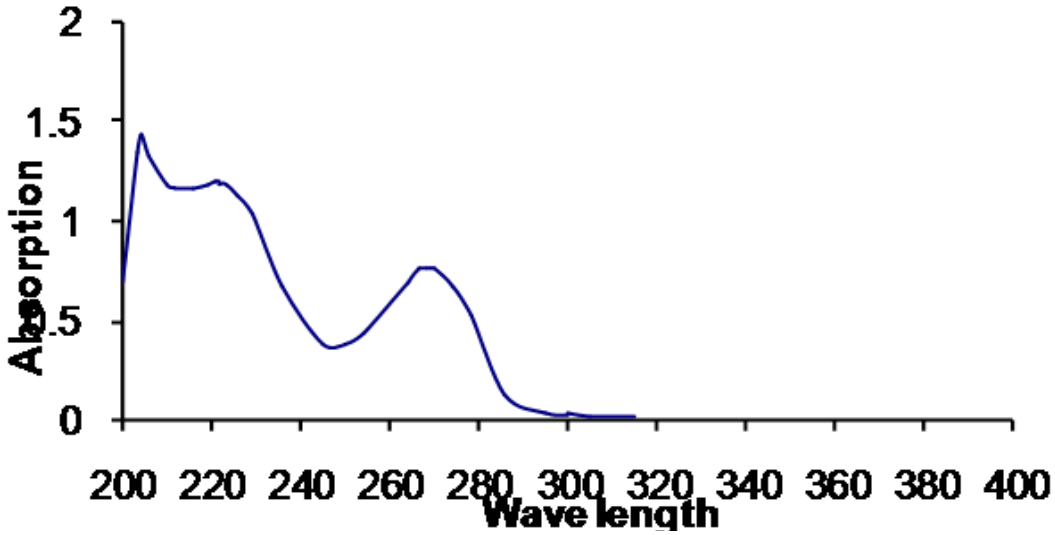

Figure 1: Spectra of Pioglitazone HCl in 0.1 N HCl

- **By infra-red spectrum method**

Drug and polymers identified by infra-red spectrum which was compared with its standard IR. The IR spectrum given below shown that the peaks obtained in the test spectrum was similar to that given in standard.

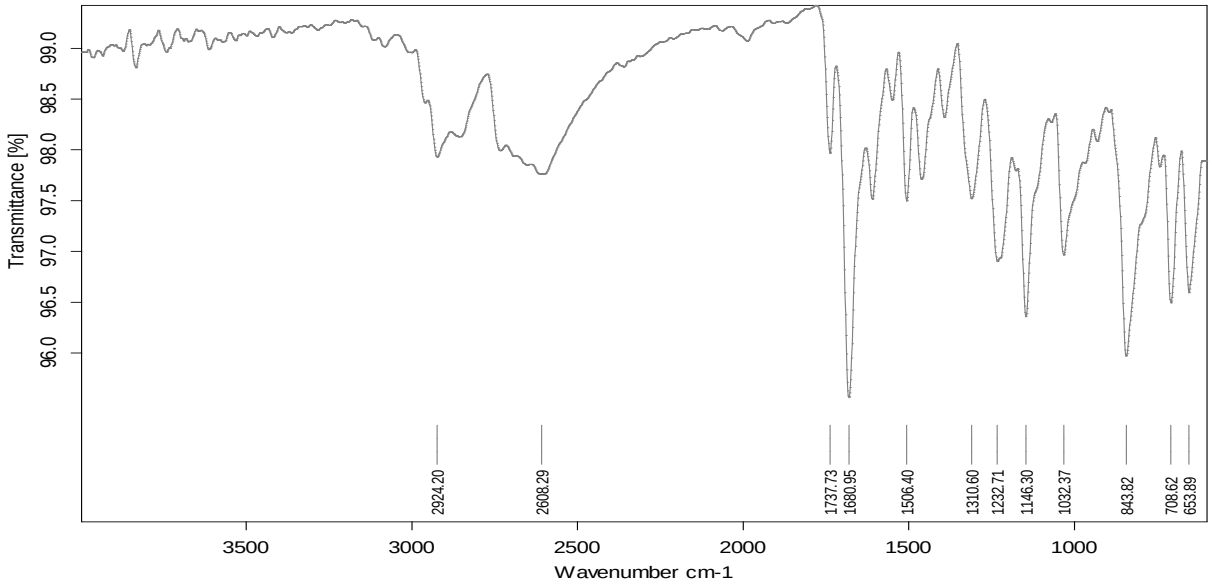

Figure 2: FT IR spectrum of Pioglitazone (Fresh Sample)

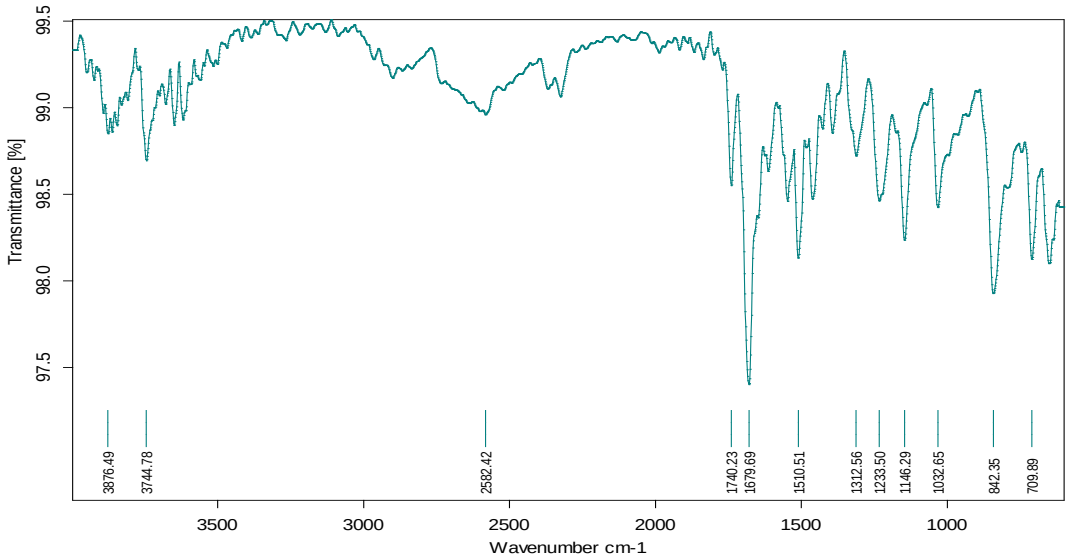

Figure 3: FT IR spectrum of Pioglitazone (After 15 days)

The Infrared spectra of Pioglitazone hydrochloride were recorded between 600to3500cm^{-1} on FTIR. From the FTIR studies at 1605.1 and 1742.23 are the characteristics peaks of Pioglitazone Hydrochloride. Peaks obtained in spectrum of pure drug (fresh & after 15 days) were similar to that given in standard.

Drug- excipients compatibility study by FTIR

Drug and excipients were accurately weighed and mixed and the resulting mixtures were scaled in screw glass vials and kept at a 50°C for 15 days The possible interaction between the drug and excipients were studied by Infra-red spectroscopy. Below spectrum shows the peaks of pure drug sample and polymers as compare to standard drug sample i.e. no chemical reaction occurs between polymers and drug samples.

Table 4 : Drug – Excipient Compatibility Studies

S. No.	API and Excipient	Drug : Excipient Ratio	Quantity per vial (mg)	No. of Vials	
				Initial	50^{0}C After 15 days
1	Pioglitazone + Eudragit RS 100	1:1	10	1	1
2	Pioglitazone + Ethyl cellulose	1:1	10	1	1
3	Pioglitazone + Xanthan gum	1:1	10	1	1

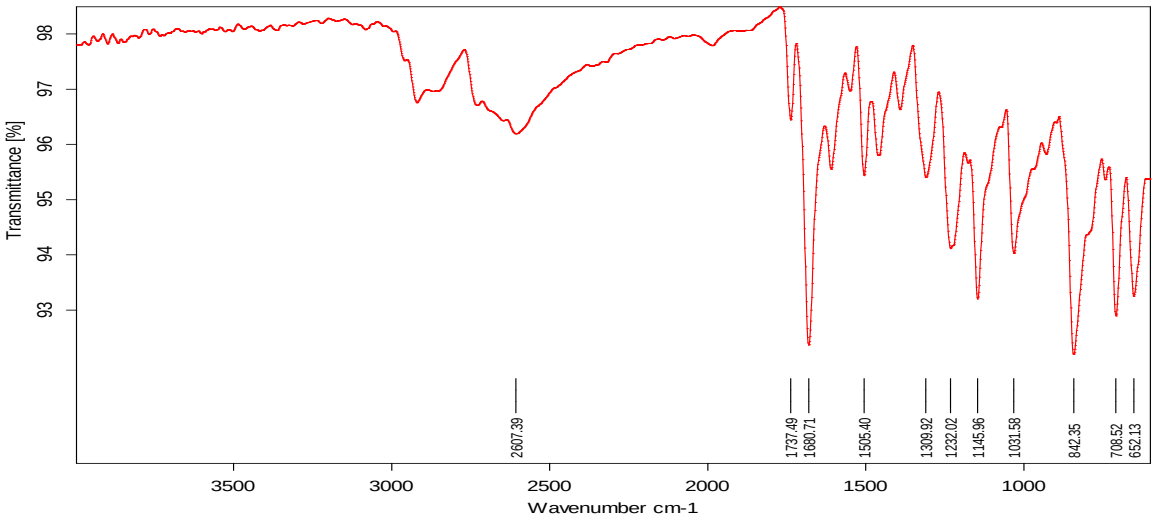

Figure 4: FT IR Spectrum of Pioglitazone with Eudragit RS 100 (Fresh Sample)

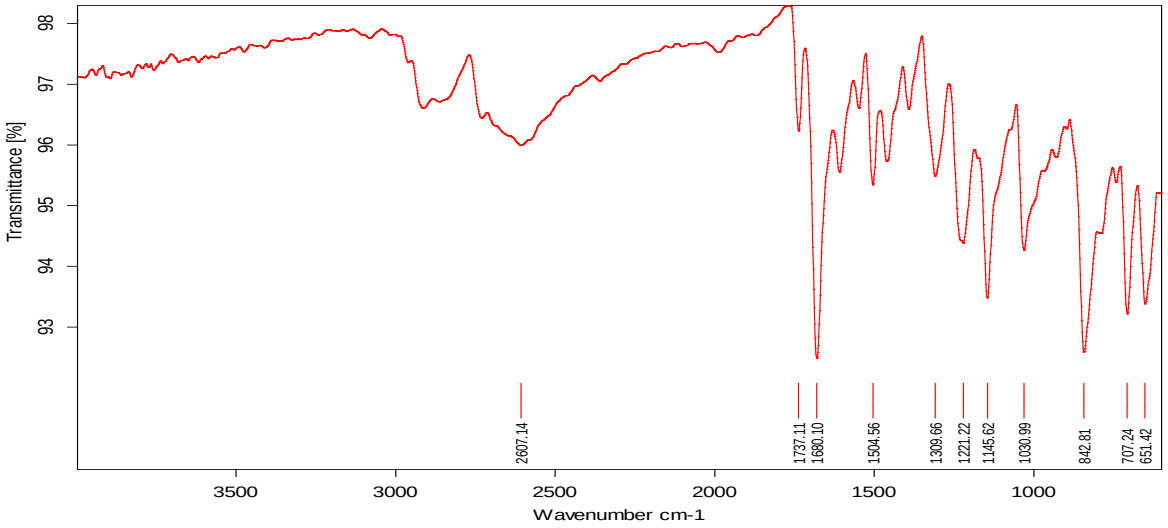

Figure 5: FT IR Spectrum of Pioglitazone with Eudragit RS 100 (After 15 days)

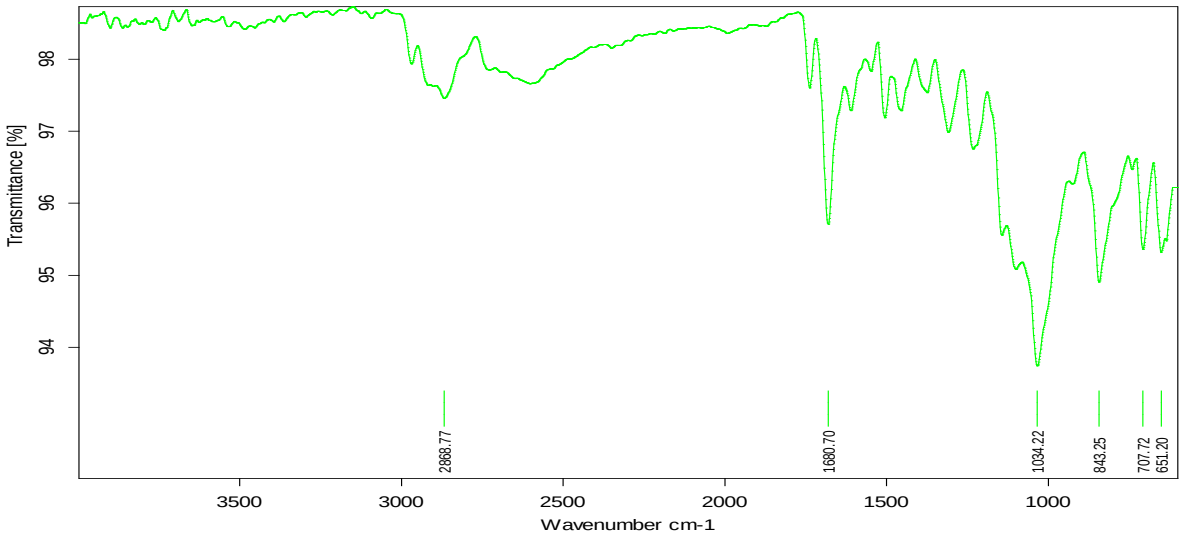

Figure 6: FT IR Spectrum of Pioglitazone with Ethyl cellulose (Fresh Sample)

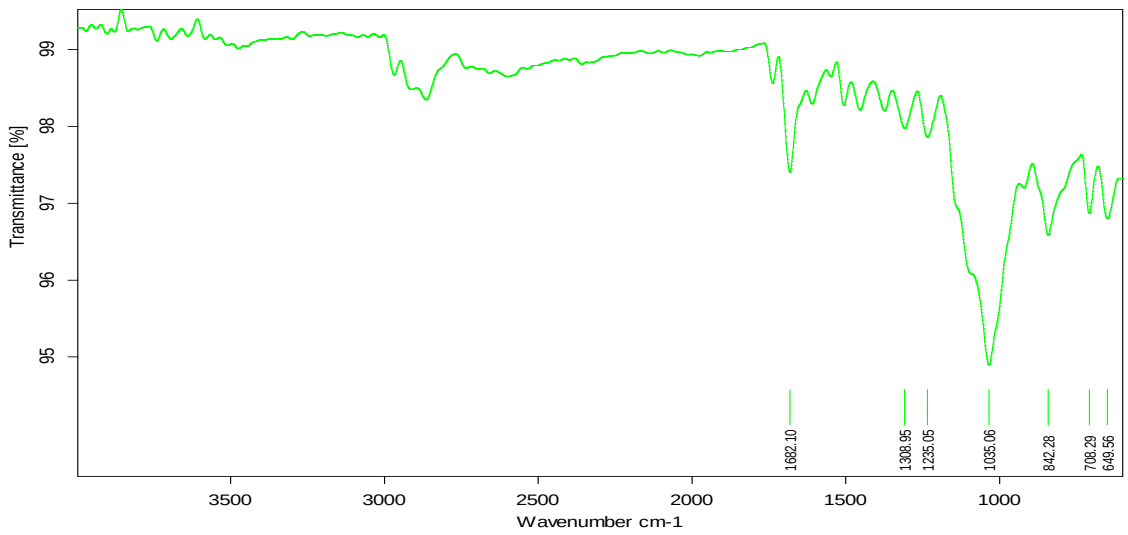

Figure 7: FT IR Spectrum of Pioglitazone with Ethyl cellulose (After 15 days)

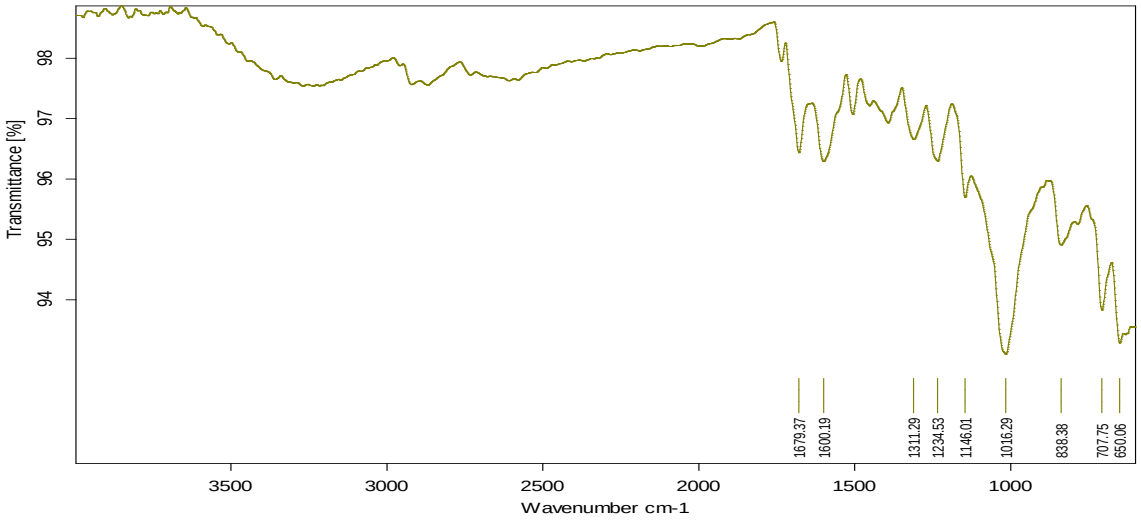

Figure 8: FT IR Spectrum of Pioglitazone with Xanthan Gum (Fresh Sample)

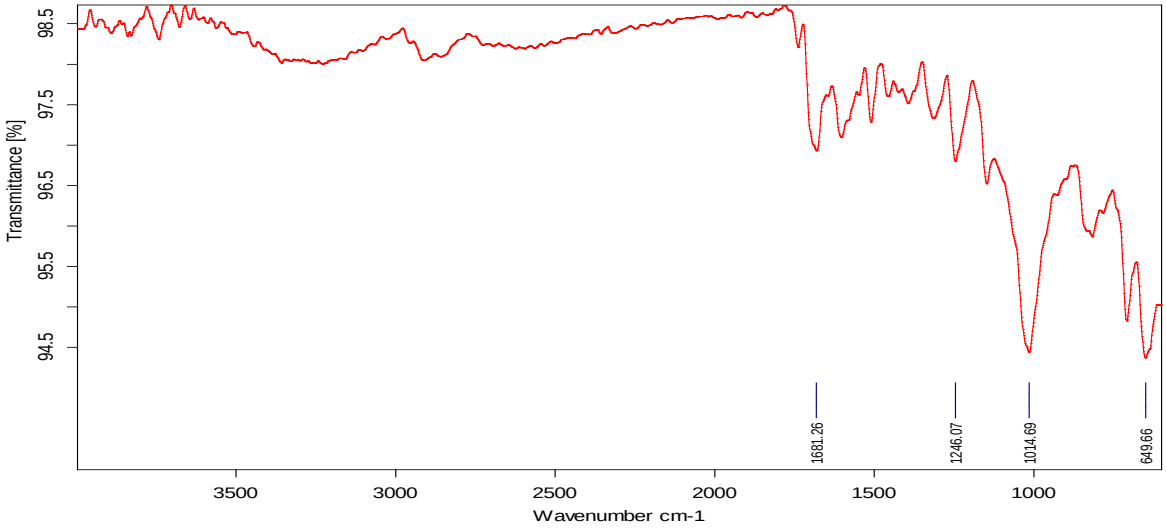

Figure 9: FT IR Spectrum of Pioglitazone with Xanthan Gum (After 15 days)

Preparation of standard calibration curve: Obtained absorbance was shown in the tables and standard calibration curves of Pioglitazone in different solvents of varying pH were shown in figures 10-11.

Table 5: Standard calibration curve in 0.1N HCl at λ_{max} 269.4nm

Concentration(µg/ml)	Absorbance (nm)
5	0.168
10	0.205
20	0.446
30	0.706
40	0.976
50	1.251

Table 6: Standard calibration curve in Phosphate buffer 7.4 at λ_{max} 269.4 nm

Concentration(µg/ml)	Absorbance (nm)
2	0.323
4	0.365
8	0.484
12	0.538
16	0.691
20	0.747

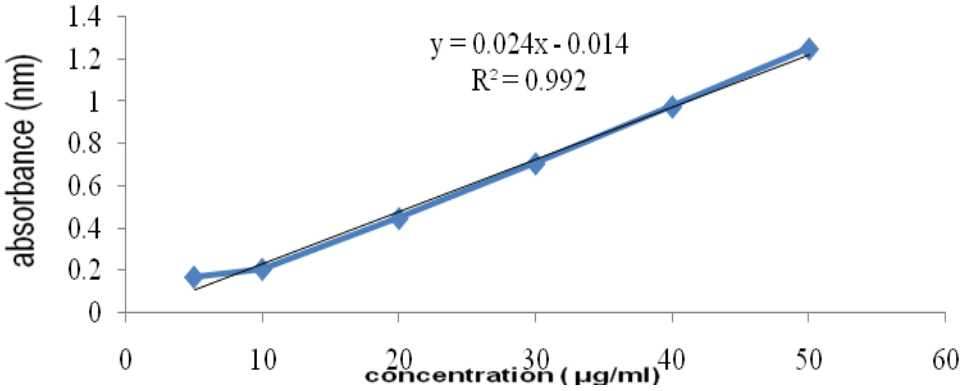

Figure 10: Standard calibration curve in 0.1N HCl at λ_{max} 269.4 nm

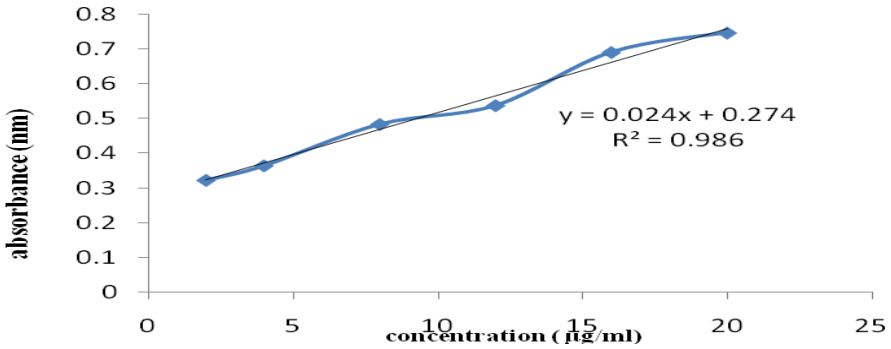

Figure 11: Standard calibration curve in phosphate buffer pH 7.4 at λ_{max} 269.4 nm

Table 7: Composition floating matrix tablets of Pioglitazone

Formulation Batch (mg)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
Pioglitazone	30	30	30	30	30	30	30	30	30	30
Carbopol 974	-	20	20	20	10	-	20	20	-	-
Eudragit RS100	-	-	20	20	10	30	20	20	25	35
Ethyl cellulose	20	20	20	-	10	30	-	-	35	25
Xanthan gum	30	20	-	-	20	-	5	10	10	10
Sodium alginate	20	20	-	-	10	-	-	-	-	-
Sodium bi carbonate	-	-	20	30	30	20	25	20	10	10
Lactose	44	34	34	44	24	34	44	44	34	34
Magnesium Stearate	3	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3	3

Table 8: Percentage Practical yield of the prepared granules

Formulation Batch	Initial Weight of Ingredients (mg)	Theoretical Yield (mg)	Yield of Formulation (mg)	% Yield
F_1	500	500	356	71.20
F_2	500	500	232	46.40
F_3	500	500	206	41.20
F_4	500	500	404.7	80.94
F_5	500	500	370.6	74.12
F_6	500	500	412.4	82.50
F_7	500	500	352.9	70.58
F_8	500	500	417.7	83.54
F_9	500	500	445.6	89.12
F_{10}	500	500	415.7	83.14

Determination of Drug Content

Table 9: Drug content of formulation batches

Formulation Batch	Drug Content
F_1	85.27%
F_2	89.23%
F_3	86.49%
F_4	92.73%
F_5	93.36%
F_6	96.12%
F_7	93.09%
F_8	96.69%
F_9	98.79%
F_{10}	94.36%

In vitro buoyancy studies

Table 10: Floating lag time of formulation batches

Formulation Code	Floating lag time (in min.)	Total Floating Time (hours)
F_1	5 min.	14
F_2	6 min. 20 sec.	20
F_3	4 min.	18
F_4	7 min. 34 sec.	> 24
F_5	3 min. 20 sec.	16
F_6	11 min. 36 sec.	22
F_7	8 min. 48 sec.	15
F_8	13 min. 19 sec.	> 24
F_9	20 min. 16 sec.	> 24
F_{10}	16 min. 01 sec	> 24

Figure 12: Floating lag time of formulation Precompression Parameters Micromeritic evaluation

Table 11: Flow properties of the powder blend

Formulation Batch	Tapped Density (g/ml)	Bulk Density (g/ml)	Compressibility Index $(\frac{\rho_t - \rho_b}{\rho_t} \times 100)$	Angle of Repose	Hausner's Ratio
F_1-F_5	0.397-0.405	0.341-0.352	13.08-14.10±0.47	28°10"- 29°33"±1.48	1.15-1.16±0.010
F_6-F_{10}	0.713-0.716	0.622-0.625	12.46-12.84±0.20	26°05"- 27°05"±0.52	1.14–1.15±0.022

Table 12: Post Compressions parameters

Formulation Batch	Diameter* (mm)	Thickness* (mm)	Hardness* (kg/cm^2)	% weight Variation* (mg)	Friability* (%)
F_1	6.10±0.28	3.83±0.18	7.20±0.25	155.00±3.00	0.78
F_2	6.08±0.53	3.65±0.10	8.00±0.45	162.20±2.81	0.83
F_3	6.08±0.26	3.68±0.14	8.50±0.72	152.35±3.76	0.48

F_4	6.06±0.45	3.73±0.08	7.50±0.24	158.25±3.24	0.65
F_5	6.09±0.22	3.83±0.02	6.30±0.11	148.55±4.11	0.58
F_6	6.09±0.28	3.46±0.21	8.20±0.30	159.80±2.16	0.86
F_7	6.08±0.51	3.74±0.40	7.25±0.15	162.30±3.83	0.61
F_8	6.10±0.35	3.79±0.32	6.35±0.22	143.45±4.01	0.42
F_9	6.09±0.04	3.81±0.30	8.16±0.40	155.50±3.12	0.64
F_{10}	6.08±0.10	3.86±0.26	8.25±0.35	156.23±2.16	0.80

*** Average of three ± Standard Deviation**

Table 13: In vitro Dissolution Profile of Pioglitazone Floating Tablet in 0.1 N HCl

Cumulative % Release at Different Time Intervals										
Time	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**	**F_{10}**
0 min.	0	0	0	0	0	0	0	0	0	0
15 min.	26.25	19.25	1.75	11.62	19.50	16.87	54.25	59.00	13.00	15.87
30 min.	20.14	15.60	1.76	19.43	22.23	19.09	55.05	61.70	13.19	19.83
45 min.	19.00	17.69	3.75	29.29	23.10	22.32	54.98	64.29	14.77	21.82
60 min.	20.61	20.29	6.52	31.20	28.48	24.69	59.78	66.52	15.97	23.44
90 min.	21.97	20.65	15.93	38.50	28.38	28.83	60.85	68.76	16.18	24.32
120 min.	22.21	24.51	17.27	41.46	29.04	28.99	61.19	69.63	21.15	28.32
3 hrs.	27.21	26.89	18.62	44.56	27.57	38.39	64.01	72.63	28.64	32.73
4 hrs.	33.23	31.04	11.97	59.56	31.85	43.10	64.49	75.15	30.92	34.28
5 hrs.	39.16	35.08	19.78	64.50	35.64	50.71	66.08	75.80	34.59	35.59
6 hrs.	44.87	39.27	25.14	67.73	45.33	54.86	69.94	78.83	37.15	36.28
7 hrs.	48.36	45.11	31.65	70.85	52.45	60.41	70.56	76.75	40.35	37.23
8 hrs.	51.37	50.60	34.45	73.98	56.49	64.98	89.18	79.03	46.19	39.18
10 hrs.	54.53	56.62	35.64	75.12	65.04	71.46	90.16	81.45	51.32	44.63
12 hrs.	61.32	64.93	41.83	77.90	70.26	73.72	90.63	85.75	62.84	48.62
16 hrs.	65.90	68.15	48.55	79.69	72.52	77.73	91.99	89.20	69.62	64.01
20 hrs.	74.62	79.39	59.44	84.48	81.65	90.27	92.47	92.16	93.04	80.35
24 hrs.	79.89	81.19	60.76	85.18	82.96	90.88	93.08	92.89	94.33	85.65

In vitro dissolution studies of all the formulations of floating tablets were carried out in 0.1N HCl solution. It was observed that the type of polymer influences the drug release pattern. These polymers showed sustained release and gastric retention of drug. This showed that increase the concentration of hydrophobic polymer give sustained release. The plot of cumulative percentage drug release V/s time (hr.) for all formulations was plotted and depicted in figure 13 respectively.

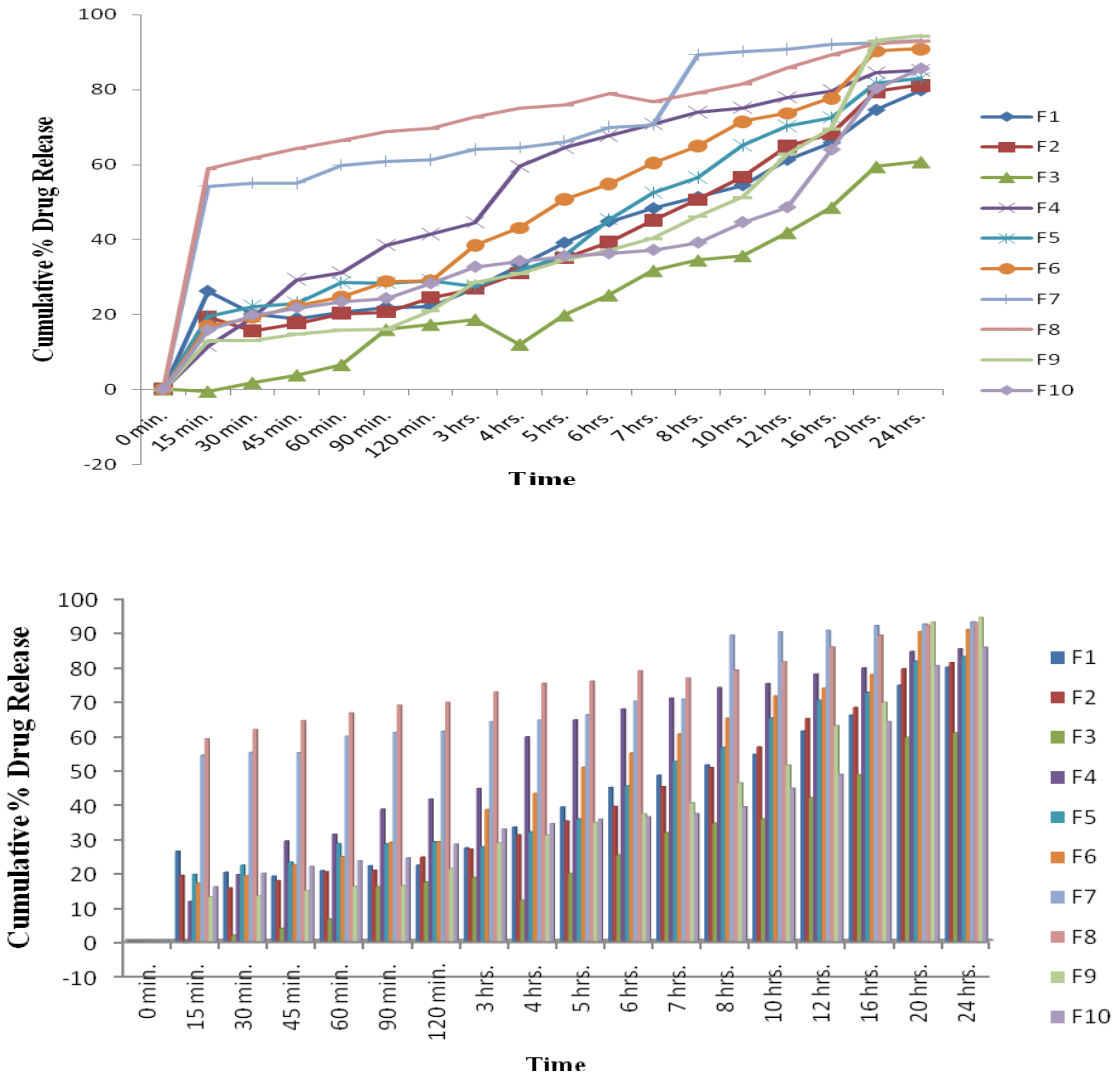

Figure 13: Comparative Dissolution Profile Data of all Formulations

As per as the percentage yield, drug content and dissolution studies was concerned, it indicated that F_9 formulation gives best percentage practical yield, and drug content shows best dissolution release. By the result observation, it can conclude that F_9 formulation should be a better candidate for floating tablet with best output.

Swelling study

Swelling study was peformed on F_9 formulation and the results of swelling index is given in table while the plot of % swelling index vs. time (hrs) is depicted in Figure 14. From the results it was concluded that when time increases, the swelling index was also increased, because weight gain by tablet increased proportionally with rate of hydration. The optimized formulations F_9 show maximum swelling index hence retarded the release of the drug for a greater time.

Table 14: Results of Swelling Index Studies of Pioglitazone Floating Tablets

Swelling index (%) at Different Time Intervals												
Time (hrs.)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
F_9	23	34	42	48	58	64	69	76	84	92	96	98

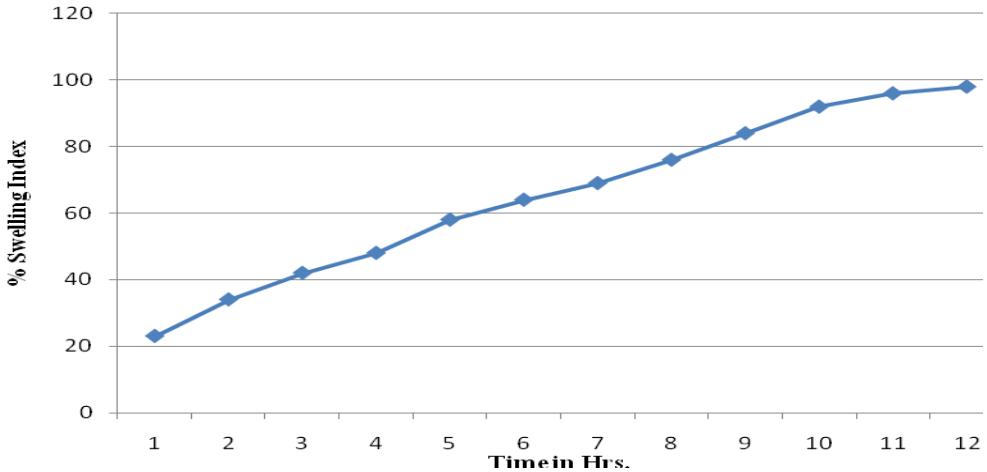

Figure 14: % Swelling Index

Release kinetics

Pioglitazone release from the floating tablets was studied in 0.1N hydrochloric acid. Pioglitazone release from all the floating tablets prepared was slow and spread over 24 h and depended on the polymer used and composition of the tablets. Release data were analyzed by zero order, first order, Higuchi and Peppas equation models as shown in table 15 and fig 15.

Table 15: Release kinetics of Pioglitazone tablet from formulation F_9

Time	Square root of time	log time	%CDR	log % CDR	log % CDR remaining
0 min.	0	0	0	0	0
15 min.	0.5	-0.602	12.12	1.08350262	1.943890048
30 min.	0.707	-0.301	13.19	1.120244796	1.938569756
45 min.	0.866	-0.1249	14.26	1.154119526	1.933183479
60 min.	1	0	16.34	1.213252052	1.92251786
90 min.	1.2247	0.17609	18.43	1.265525335	1.911530462
120 min	1.416	0.301	22.53	1.352761192	1.889133556
3 hr.	1.732	0.4771	27.90	1.445604203	1.857935265
4 hr.	2	0.602	32.18	1.50758604	1.831357785
5 hr.	2.206	0.6989	34.60	1.539076099	1.815577748
6 hr.	2.449	0.7781	36.42	1.561339941	1.803320524
7 hr.	2.645	0.845	40.36	1.605951158	1.775537635
8 hr.	2.828	0.903	45.83	1.661149857	1.733758836
10 hr.	3.162	1	52.58	1.720820582	1.67596155
12 hr.	3.464	1.0791	56.36	1.750970984	1.639884742

16 hr.	4	1.204	69.66	1.84298347	1.482015576
20 hr.	4.472	1.301	87.91	1.94403828	1.082426301
24 hr.	4.898	1.3802	95.26	1.978910577	0.675778342

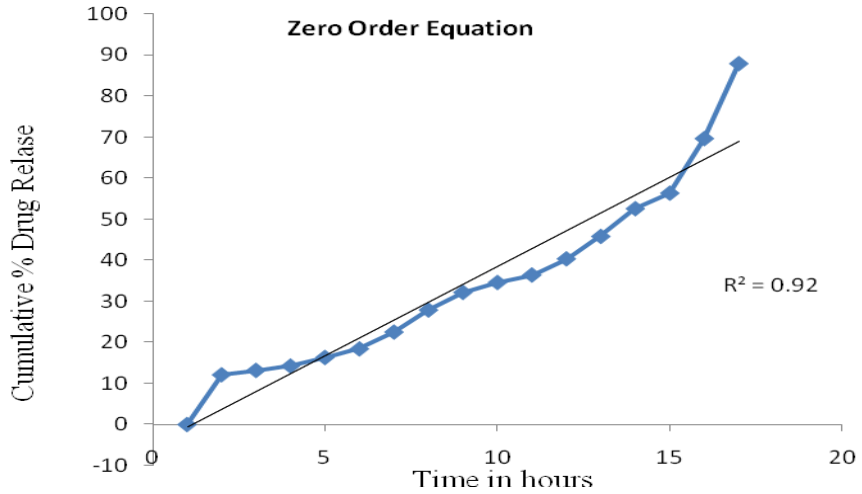

Figure 15 : Zero order release kinetics of Formulation F_9

The presently preferred route of administration for Pioglitazone hydrochloride was oral route. In the present work efforts have been made to develop floating drug delivery system for Pioglitazone hydrochloride containing Ethyl cellulose and Eudragit RS 100. The FTIR spectral analysis showed that there was no appearance or disappearance of any characteristic peaks of pure drug in the physical mixture of drug and polymer which confirms the absence of chemical interaction between drug and polymers. The granules were prepared by wet granulation method and the granules of all formulation were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and drug content. The result indicates the granules were having a good free flowing property suitable for tablet formulation. The tablets of all formulation were subjected to various evaluation parameters such as thickness, diameter, weight variation, hardness, friability, drug content, in-vitro buoyancy lag time, total floating time, tablet density, swelling index and in-vitro dissolution study. The results of all these tests were found to be satisfactory. The results of in vitro drug release studies show that F_9 has better-sustained release than the other formulations. The formulations showed higher R^2 values for zero order plots indicating that drug release followed zero order kinetics.

CONCLUSION

The present study showed that F_9 formulation (Ethyl Cellulose, Xanthan gum and Eudragit RS100) gives best percentage yield, drug content and shows best dissolution release. So it

was conclude that F_9 formulation should be a better candidate for floating tablet with best output. It can be conclusively stated that the gastric floating tablet appears to be a promising system for the delivery of sustained release Pioglitazone for the treatment of diabetes.

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