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DESIGN AND EVALUATION OF PIOLGLITAZONE HCL SUSTAINED RELEASE TABETS FOR TYPE 2 DIABETES MELLITUS

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ABSTRACT

The objective of this study is to formulate and evaluate sustained release tablets of Pioglitazone HCl, which were developed to prolong the action leading to an increase in drug bioavailability and reduced dosing frequency. Sustained release (SR) drug delivery systems are developed to modulate the release of drug, in order to achieve specific clinical objectives that cannot be attained with conventional dosage forms. Possible therapeutic benefits of a properly designed SR dosage form include low cost, simple processing, improved efficacy, reduced adverse events and flexibility in terms of the range of release profiles attainable. Two different grades of HPMC K 100M, HPMC K15M and PEO, carbopol, Xanthum gum, MCC, Magnesium stearate and talc were used as variants along with pioglitazone HCl as active pharmaceutical ingredient. All these polymers are used in different concentrations to sustain the action. The tablets were prepared by direct compression method and are evaluated for pre compressional studies like bulk density, tapped density, compressibility index, Hausner ratio and angle of repose; all the values were found within limits of standard. *In vitro* release studies were carried out by USP type II paddle apparatus. The interaction of polymer and drug ruled out by FTIR studies. The FTIR studies confirmed that there is no interaction between the drug and polymer. Data of in-vitro release of tablets were fit in different equations and kinetic models to explain release kinetics the models used were zero order and first order equations. Higuchi and Korsmeyer peppas models based on physiochemical properties and *in vitro* release studies. The results showed that HPMC K15M produce sustained release of drug. The formulation F10 (HPMCK15M) with 1:3 ratio produced 99% drug release at 12 h.

Key words: Sustained release dosage form, HPMC K100M, HPMC K15M, PEO, Carbopol, Xanthan gum, Release kinetics

INTRODUCTION

Sustained drug Delivery

A sustained release dosage form delivers the drug in a predictable, pre-programmed, pre-determined controlled rate and at specific intervals for a longer period. The aim of sustained and controlled delivery of drugs is to achieve a convenient, self-administered dosage form that yields a constant infusion of the drug for a long time [1]. This type of drug delivery system is known to provide a prompt release of drug. Therefore, to achieve as well as to maintain the drug concentration within the therapeutically effective range needed for treatment, it is often necessary to take the conventional type of drug delivery systems several times a day. This results in a significant fluctuation of drug levels in the body [2,3].

Pathophysiological state of subject play important part in the design of suitable controlled release delivery system that is in hepatic failure oral delivery of drug should be stopped. The following table enlists the various drug related and biological factors affecting the design and *In vivo* performance of controlled release formulations [4].

An overview of matrix controlled oral release system [5-8]

Oral controlled release dosage forms can be classified in different ways. One way is to distinguish between single-unit dosage forms such as tablets and capsules, and multi-particulate dosage forms such as pellets or beads.

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Oral sustained release technologies may be classified according to different criteria including the type of release (e.g. continuous release, delayed transit release, slow, prolonged, pulsed, repeat-action, etc.), the release mechanism (e.g. diffusion, dissolution, etc.) Controlled release products can be classified as i) Reservoir systems including enteric coated tablets, capsules, coated granules and microcapsules. ii) Osmotic systems, iii) Ion-exchange resins, iv) Matrix systems. Release from inert matrix tablets occurs via a leaching mechanism.

Drug particles dispersed in the polymer matrix dissolve in the penetrating gastro-intestinal fluids and are released from the tablet by diffusion through the porous network of already existing pores and pores that created by dissolution of the drug particles. At drug loadings exceeding approximately 10-15 % volume, a continuous structure connecting all drug particles exists (percolating drug network). At considerably lower loadings, a particular fraction of the drug may be completely surrounded by the polymer matrix (trapped fraction), which would result in incomplete release.

Diabetes and anti-diabetic drugs [9]

Diabetes develops when the level of blood sugar increases due to insufficient or ineffective insulin secreted from the pancreas. Blood sugar is then released via urination, leading to "sugary urine", or diabetes. The disease may give rise to multiple complications such as cardiovascular disease, nerve damage, kidney damage, eye damage, foot ulcer, etc., and in severe cases, coma. Patients must receive long-term treatment to maintain the stability in blood sugar, thereby reducing the risk of complications. The term diabetes mellitus describes a metabolic disorder of multiple etiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long term damage, dysfunction and failure of various organs.

Anti-diabetic Drugs classification and mechanism of action [10]

Insulin; Alpha-glucosidase inhibitors (starch inhibitors): Block intestinal starch absorption. Acarbose and Miglitol; Sulfonylureas: Acute release of insulin by functioning beta cells of pancreatic islet tissue; Increase insulin sensitivity. Glimepiride, Glyburide, Chlorpropamide, Acetohexamide, Olipazide, Glyburide, Tolbutamide, Tolazamide; Biguanides: Reduces hepatic glucose overproduction, Increases insulin receptors and Decreased intestinal absorption of glucose. Metformin hydrochloride; Thizolidinediones: Affects Liver, Muscle, and Fat Decreases insulin resistance Increases glucose uptake, Decreased hepatic glucose production, Affects PPARs (peroxizome proliferated activated receptors) - creates liver side effects. Piglitazone and Rosiglitazone; Insulin secretagogues: Enhances insulin secretion by functioning pancreas. Repaglinide and Nateglinide.

REVIEW OF LITERATURE

Crowley M et al [11] investigated the drug release mechanism from ethyl cellulose matrix tablets prepared by direct compression (or) hot-melt extrusion (HME) of binary mixtures of water soluble drug (guaifenesin)and the polymer. Guaifenesin release rate dependent upon the partical size of ethyl cellulose. They found that the tablets prepared by hot-melt extrusion exhibited considerably slower drug release relatively than those prepared by direct compression. Ravi PR et al [12] carried out oral controlled release matrix tablets of Zidovudine (AZT) using HPMC, Ethyl cellulose, Carbopol 971 P and to study the effect of various formulation factors on in-vitro drug release. Release studies were carried using USP type 1 apparatus in 900 ml of dissolution media. CR matrix tablets of AZT were prepared by wet granulation method. The release rate decreased with increase in polymer proportion and compression force. The release rate was fastest for formulations containing Ethylcellulose, as it remained intact over the drug release period and no swelling was observed, indicating that the release was controlled.

Himansu et al [13] developed oral sustained release matrix tablets of an antiretroviral drug, zidovudine. Matrix tablets were prepared by wet granulation method using various proportions of hydrophilic polymers like Sodium CMC, HPMC, Eudragit-L155, Xanthan gum alone or in combination with hydrophobic polymer ethyl cellulose. The release kinetics was analyzed using zero order, first order, Higuchi and Hixson Crowell model. From this study it was concluded that presence of sodium CMC gives zero-order release kinetics and the linearity ranges from 0.990 to 0.996. It has also good drug entrapment efficiency ranging from 96 to 106% of drug. Formulation containing sodium CMC with Xanthan gum and EC gives sustained release for drug more than 12 h. Deepika V et al [14] formulated the sustained release matrix tablets of an anti-retroviral drug, zidovudine. In this the sustained release matrix tablets were prepared by wet granulation method by using hydrophilic polymers like HPMC, SCMC and Na Alginate. The optimized formulation was further modified using different hydrophobic polymers as granulating agents, such as PVP, Eudragit RL100 and Ethyl cellulose to control the drug release. They found that the hydrophilic matrix of HPMC alone could not control the antiretroviral drug release effectively for 12 h. Kinetic treatment to the *In vitro* release data revealed that the drug release followed first order release and mechanism of drug release is by Non-fickian transport. Hence the based on the previous literature review the work was designed to develop and formulate sustain release tablets of anti-diabetic drug, to evaluate the formulated dosage forms by official *in-vitro* studies.

MATERIALS

Pioglitazone HCl was procured as gift samples from Pharma Train, (Hyderabad), HPMC K100M, HPMC K15M, Polyethylene oxide, Xanthan gum, Magnesium Sterate and MCC from Dow Chemical Co., (USA), Carbopol 934 P was supplied by Colorcon, (UK), PVP K30 from Peter Greven, (Netherlands), Methanol and ethanol from S.D. Fine Chemicals (Mumbai), All the materials used in the study were of analytical and laboratory grade.

METHODS

Phosphate buffer (pH 6.8) solution: Take 6.8gm of potassium di-hydrogen phosphate (KH_2PO_4) and dissolve it in 1000ml of water and stir it. Then, add 0.9 gm of NaOH, mix it well. It will give a pH of 6.8. *Preparation of 0.1N HCl solution*: 8.33 ml of concentrated HCl and transferred into a volumetric flask. Then dilute volume (1L) with water [15].

Analytical Methods [16,17]

Determination of λ max of pioglitazone HCl in 0.1N HCl solution

For the assessment of drug in the assay and dissolution testing, UV spectrophotometric method was developed. The drug solutions of various concentrations prepared were scanned for λ max form 200-400 nm in a UV/Visible spectrophotometer was recorded.

Calibration curve of pioglitazone in 0.1N HCl solution

Pioglitazone content was estimated by measuring the absorbance at 269nm. The standard curve for Pioglitazone was prepared with 0.1N HCl. The method obeyed Beer's law in the concentration range of 2 to 10 µg/ml. Procedure: 100mg of Pioglitazone was weighed and dissolved in 0.1N HCl (30ml) and then made up to a volume of 100ml with 0.1N HCl. From the stock solution 10 ml was diluted to 100 ml with 0.1N HCl. Several dilutions were made from this stock solution, to obtain a concentration range of 2 to 10 µg/ml. The absorbance was measured at 269 nm

PRE AND POST FORMULATION STUDIES

Determination of melting point

Melting point of the drug was determined by taking small amount of drug in a capillary tube closed at one end. The capillary tube was placed in a melting point apparatus and the temperature at which drug melts was recorded. This was performed thrice and average value was noted.

Determination of solubility [18]

The solubility of drug sample was carried out in different solvents (aqueous and organic) according to the United States of pharmacopoeia. The result is then compared with those given in the United States pharmacopoeia. Solubility can be determined by placing the drug in a vial along with the solvent. The tightly closed vial is then agitated at constant temperature and the amount of drug in solution is determined periodically by assay of filtrate sample of the supernatant. Solubility of drug substance was performed in purified water, 0.1N HCL, and phosphate buffer pH6.8. 50mg of pioglitazone was weight and solubility of this sample was checked in water, methanol and phosphate buffer.

Drug and excipients compatibility

The objective of drug/excipients compatibility considerations and practical studies is to delineate, as quickly as possible, real and possible interactions between potential formulation excipients and the API. This is an important risk reduction exercise early in formulation development. Homogenous mixtures of drug and excipients were prepared and filled in glass vials and self-seal LDPE (Low Density Poly Ethylene) bags. Chemical compatibility is tested by FTIR spectroscopy, which is most widely used technique to identify functional interactions of the drug with polymer if any. The two methods employed are open vial and closed vial with rubber stopper [19].

Formulation of Pioglitazone Sustained Release Tablets by Direct Compression

The sustained release Matrix tablets containing drug were prepared by sifting the API and diluent through #40 sieve followed by sifting of all other polymers and excipients via # 40 sieve. All the ingredients were mixed by geometric dilution technique to ensure uniform mixing. The blend of Mixing drug, polymer and excipients is mixed again sifted through # 60 mesh and blended for 15 min in blender. Later on the above blend is mixed for 5 min with sifted Magnesium stearate for increasing the flow of blend. Later the prepared blend was subjected to direct compression using Tablet Punching Machine with 4-6 kg/cm^2 hardness of tablet using 9.5 mm round, flat and plain punches on a single/ multi stroke punching machine.

Evaluation of Rheological Characteristics

Angle of Repose

The flow property was determined by measuring the Angle of Repose. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal plane [20].

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

Where, h = height, r = radius, θ = angle of repose.

Angle of repose was determined by measuring the height, radius of the heap of the powder. A cut system funnel was fixed to a stand and bottom of the funnel was fixed at a height of 3 cm from the plane. Powder was placed in funnel and allowed to flow freely and measured the height and radius of the heap. Similar studies were carried out after incorporating lubricants / glidants. The sample was passed through the funnel slowly to form a heap. The height of the power heap formed was measured;

the circumference formed was drawn with a pencil on the graph paper. The radius was measured and the angle of repose was determined. This was repeated three times for a sample

Compressibility Index

The flow property was also determined by measuring the compressibility index (I) by application of a compressibility index (I) given by equation [21]. CI = [1 – (V/V_0)] x 100; Where 'V' the volume occupied by a sample of the powder after being subjected to a standardized tapping procedure (after 500 vibrations) and 'V_0' in the volume before tapping. 10gms of the final blend was taken in a 50 ml – measuring cylinder. Measured the initial volume before tapping of the three measuring cylinder. After 500 tappings, occupied volume was determined for the measuring cylinder. The compressibility index (I) was determined by using above equation.

Bulk Density

A bulk density is defined as the ratio of mass of the drug and its bulk volume. Exactly 50gm of drug were weighed on digital balance and transferred into a 100ml measuring cylinder. The volume occupied by the drug was recorded as the bulk volume. The bulk volume and the bulk density was calculated as follows [22]. Bulk density = Weight of sample / Volume occupied by the sample (ml).

Tapped Density

Weighed an accurately 50 gm of pure drug were weighed on digital balance and transferred into a 100ml measuring cylinder. The cylinder was tapped on the wooden platform until the volumes occupied was remian constant. This is tapped volume and the tapped density was calculated. It is expressed in g/cc and is given by, Tb (gm/cc) = M / Vt, where M is the mass of drug in gm and Vb is the bulk volume of the drug [23]. Tapped density (g/ml) = Weight of the powder / Volume occupied by the sample (ml)

Post Compressional Evaluation of Pioglitazone Sustained Release Tablets

Weight Variation [24]

The USP weight variation test was run by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weights to the average. The tablets met the USP tests that were no more than 2 tablets were outside the percentage limit and no tablets differed by more than 2 times the percentage limit.

Weight Variation Tolerance For Uncoated Tablets		
S.No.	**Average Weight of Tablets (mg)**	**Percentage Difference Allowed**
1	130 or less	10
2	130 to 324	7.5
3	More than 324	5

Hardness

Hardness of the tablets was determined by breaking it between the second and third fingers with thumb being as a fulcrum. There was a sharp snap the tablet was deemed to have acceptable strength [25]. Hardness of the tablets is also determined by Stokes Monsanto Hardness Tester and the hardness should be found within the range of 3.5-5.5 kg/cm².

Friability

The friability of tablets is determined by Roche friablator. 20 tablets were taken and weighed. After weighing the tablets were placed in the apparatus and subjected to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm for minutes dropping the from a distance of six inches with each revolution .after operation the tablets were de-dusted and reweighed [26]. Friability is determined by F=100 (1-Wo/Wt); Where, Wo= wt. of tablets before friability test. Wt= wt. of tablets after friability test.

Content Uniformity

In this test, 30 tablets were randomly selected and 20 tablets were crushed and powder equivalent to 100mg of drug was weighed and was subjected to content uniformity studies. The tablets should contain not less than 85% or more than 115% of the labeled drug content as per the test and hence was considered to be passed [27]. Twenty tablets of formulation were weighed and finely powdered. The powder equivalent to 100 mg of Pioglitazone was accurately weighed and approximately 50-60 ml of 0.1N NaOH was added and stirred until it gets dissolved and sonicated for 5-10 min. The volume of solution was made up to 100 ml. The solution was filtered. Then 10 ml of filtrate was diluted up to 100 ml with 0.1 N NaOH. 2.1 ml of resulting solution was diluted up to 10 ml. Absorbance of the final solution was recorded at 269 nm.

Thickness

The thickness of a tablet was the only dimensional variable related to the process. 10 tablets were measured for their thickness and diameter with a Caliper, Thickness Gauge. Average thickness and diameter were calculated [28,29].

***In-vitro* Dissolution of Pioglitazone SR-Tablets**

The dissolution test was carried out using USP apparatus II. Stirring speed was maintained at 50 rpm. Phosphate buffer (pH 6.8) was used as dissolution medium (900ml) and was maintained at 37 ± 0.5^0C. Samples of specified volume were withdrawn at predetermined time intervals, filtered, dilute suitably and assayed on UV spectrophotometer. An equal volume of fresh medium was immediately replaced to maintain the dissolution volume. The sample was analyzed spectrophotometrically at 269 nm. Using spectrophotometer to assay the amount of

Pioglitazone released at each time interval. Dissolution studies were performed for 12 h for each tablet formulation and the mean values were taken.

Release Kinetics

The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and it is practically evident in case of matrix system. As a model dependent approach the dissolution data are fitted to three popular release models such as zero order, first order, diffusion equations which have been described in the literature. The order of drug release from matrix system was described by zero order kinetics or first order kinetics. The mechanism of drug release from matrix system was studied by Higuchi equation [30,31]. korsemeyer peppas release model; the release rate data were fitted to the following equation. $Mt/M\infty = K.t^n$ Where, $Mt/M\infty$ is the fraction of the drug release, 'K' is the release rate constant, 't' is the release time, and "n" is the diffusion exponent for the drug release that is dependent on the shape of the matrix dosage form.

RESULTS

Compatibility studies – FT-IR method

Pioglitazone and excipients are subjected to FT-IR spectral analysis. The drug was compatible with excipients since no significant changes were observed in intensity and position of the peaks in the spectra.

Table 1. Formulation table of Pioglitazone Sustained Release Tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Pioglitazone	30	30	30	30	30	30	30	30	30	30
HPMC K100M	60	90	-	-	-	-	-	-	-	-
PEO	-	-	60	90	-	-	-	-	-	-
Carbopol	-	-	-	-	60	90	-	-	-	-
Xanthan Gum	-	-	-	-	-	-	60	90	-	-
HPMC K15M	-	-	-	-	-	-	-	-	60	90
PVPK 30	30	30	30	30	30	30	30	30	30	30
MCC	130	100	130	100	130	100	130	100	130	100
Mg. Sterate	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2
Total Weight (G)	254	254	254	254	254	254	254	254	254	254

Table 2. Pre-compression parameters of pioglitazone tablet powder blends

Formulation Code	Bulk density (Kg/cm^3)	Tapped density (Kg/cm^3)	Carr's index	Hausner's ratio	Angle of repose ($^0Ø$)
F1	0.43	0.52	17.3	1.41	12.62
F2	0.40	0.46	13.0	1.5	12.29
F3	0.50	0.58	13	1.16	11.58
F4	0.44	0.51	13.7	1.25	9.29
F5	0.39	0.47	17.0	1.56	18.23
F6	0.42	0.52	19.2	1.45	13.24
F7	0.36	0.39	7.6	1.0	11.03
F8	0.41	0.50	18	1.5	17.4
F9	0.39	0.48	18	1.23	11.96
F10	0.41	0.51	19.6	1.53	12.26

Table 3. Post compression parameters evaluation of pioglitazone tablets F1 - F10

Formulation Code	weight uniformity	Thickness± SD n=3 (mm)	% friability	%Drug Content ± SD	Hardness (Kg/cm^2) ± SD
F1	254±0.23	3.16±0.11	0.22	102.0 ±1.1	4.68 ±0.17
F2	253±0.52	3.53±0.15	0.15	101.3 ±1.5	5.13 ±0.15
F3	252±0.17	4.06±0.057	0.12	99.8±1.3	5.58 ±0.13
F4	253±0.28	5.1±0.1	0.43	101.7 ±0.8	5.98 ±0.04
F5	255±0.31	3.03±0.05	0.32	100.6±1.2	4.63 ±0.05
F6	254±0.15	3.83±0.15	0.14	98.9 ±2.1	5.2 ±0.02
F7	253±0.22	4.93±0.05	0.20	99.2± 1.7	5.7 ±0.10
F8	255±0.31	5.26±0.1	0.33	99.5± 1.4	5.93 ±0.05
F9	254±0.52	3.02±0.2	0.18	99.2±1.3	4.39 ±0.02
F10	253±0.41	3.48±0.14	0.21	100.3 ±1.4	4.86 ±0.03

Table 4. *In-vitro* drug release profiles of F1 –F10 Pioglitazone Tablets

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.00	8.70	6.83	7.22	6.83	19.00	8.90	57.68	45.00	11.48	15.00
2.00	13.16	9.03	15.92	11.22	21.00	16.26	69.89	59.00	24.00	29.00
3.00	15.87	11.74	25.42	21.00	45.00	34.00	76.26	71.00	36.00	38.00
4.00	17.90	13.29	34.97	30.00	51.00	48.00	86.00	80.00	49.00	55.00
6.00	23.35	15.35	42.19	39.00	63.00	59.00	93.00	86.00	62.00	69.00
8.00	32.50	21.80	57.00	55.00	75.00	71.00	100.00	95.00	75.00	82.00
10.00	38.00	35.00	72.00	68.00	83.00	78.00	---	100.00	84.00	93.00
12.00	46.00	41.00	83.00	76.00	89.00	81.00	---	---	91.00	99.00

Table 5. Korsemeyer peppa's plot data profiles of F1 –F10 Pioglitazone Tablets

Log T	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.000	-1.060	-1.166	-1.141	-1.166	-0.721	-1.051	-0.239	-0.347	-0.940	-0.824
0.301	-0.881	-1.044	-0.798	-0.950	-0.678	-0.789	-0.156	-0.229	-0.620	-0.538
0.477	-0.799	-0.930	-0.595	-0.678	-0.347	-0.469	-0.118	-0.149	-0.444	-0.420
0.602	-0.747	-0.876	-0.456	-0.523	-0.292	-0.319	-0.066	-0.097	-0.310	-0.260
0.778	-0.632	-0.814	-0.375	-0.409	-0.201	-0.229	-0.032	-0.066	-0.208	-0.161
0.903	-0.488	-0.662	-0.244	-0.260	-0.125	-0.149	0.000	-0.022	-0.125	-0.086
1.000	-0.420	-0.456	-0.143	-0.167	-0.081	-0.108	0.000	0.000	-0.076	-0.032
1.079	-0.337	-0.387	-0.081	-0.119	-0.051	-0.092	0.000	0.000	-0.041	-0.004

Table 6. Results of model fitting of Pioglitazone from F1 –F10 Tablet formulations

Formulation	Zero Order	First Order	Higuchi	Korsemeyer Peppas	'n' value	Best fit
F1	0.9841	0.9859	0.9505	0.0575	0.1891	First Order
F2	0.955	0.9359	0.8605	0.0362	0.1715	Zero Order
F3	0.9927	0.9589	0.9363	0.2884	0.4876	Zero Order
F4	0.994	0.9789	0.9232	0.2688	0.5013	Zero Order
F5	0.9248	0.9934	0.9723	0.304	0.3573	First Order
F6	0.9266	0.9884	0.9503	0.325	0.4946	First Order
F7	0.612	0.9372	0.8632	0.4162	0.1361	First Order
F8	0.7255	0.9697	0.9353	0.401	0.188	First Order
F9	0.9544	0.9897	0.9715	0.3461	0.4502	First Order
F10	0.9508	0.8979	0.9754	0.3777	0.4282	Higuchi

Figure 1. Schematic representation of leaching-based release mechanism

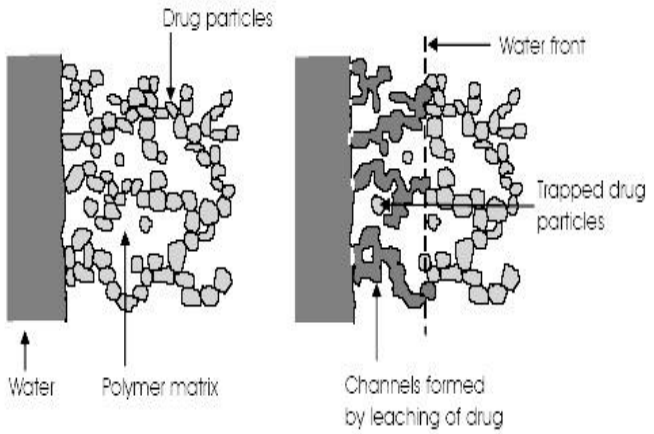


Figure 2. Biochemical diagnostic testing profile of diabetes mellitus

Values for diagnosis of diabetes mellitus and other categories of hyperglycaemia

	Glucose concentration, mmol l⁻¹ (mg dl⁻¹)		
	Whole blood		Plasma[a]
	Venous	Capillary	Venous
Diabetes Mellitus:			
Fasting	≥6.1 (≥110)	≥6.1 (≥110)	≥7.0 (≥126)
or			
2-h post glucose load	≥10.0 (≥180)	≥11.1 (≥200)	≥11.1 (≥200)
or both			
Impaired Glucose Tolerance (IGT):			
Fasting (if measured)	<6.1 (<110)	<6.1 (<110)	<7.0 (<126)
and			
2-h post glucose load	≥6.7 (≥120) and <10.0 (<180)	≥7.8 (≥140) and <11.1 (<200)	≥7.8 (≥140) and <11.1 (<200)
Impaired Fasting Glycaemia (IFG):			
Fasting	≥5.6 (≥100) and <6.1 (<110)	≥5.6 (≥100) and <6.1 (<110)	≥6.1 (≥110) and <7.0 (<126)
and (if measured)			
2-h post glucose load	<6.7 (<120)	<7.8 (<140)	<7.8 (<140)

Figure 3. Mechanism of action of thiazolidinediones in type 2 diabetes mellitus. PPARγ = peroxisome proliferator-activated receptor-gamma; TNF-α = tumour necrosis factor-α.

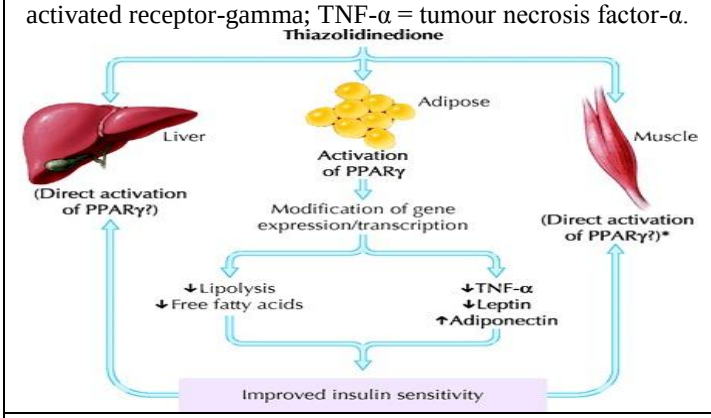


Figure 4. Calibration Curve for Pioglitazone HCl

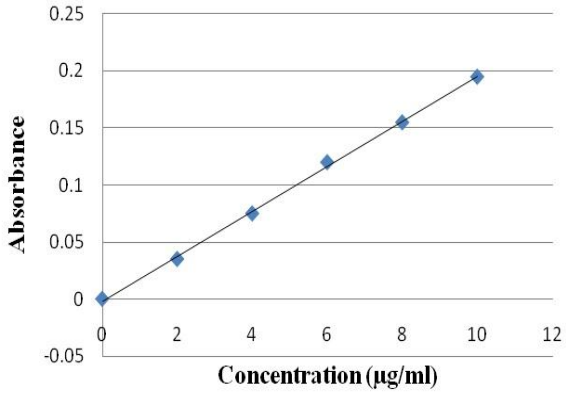


Figure 5. FTIR spectra of Pioglitazone HCl pure drug

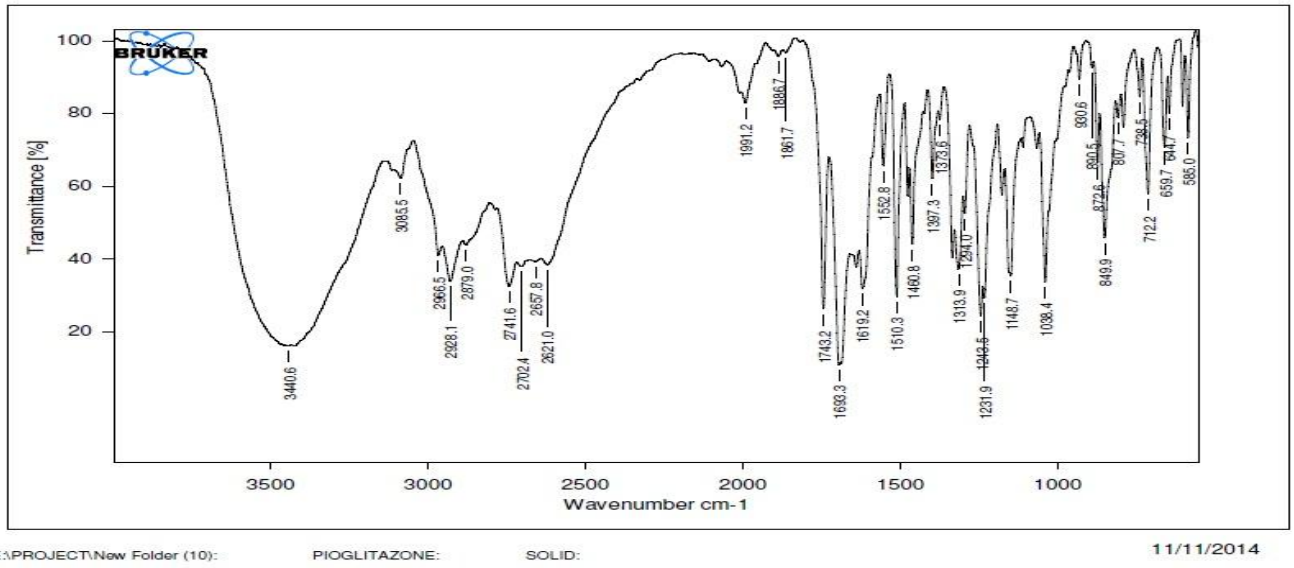


Figure 6. FTIR spectra of Pioglitazone HCl pure drug and HPMC K15 M (F10)

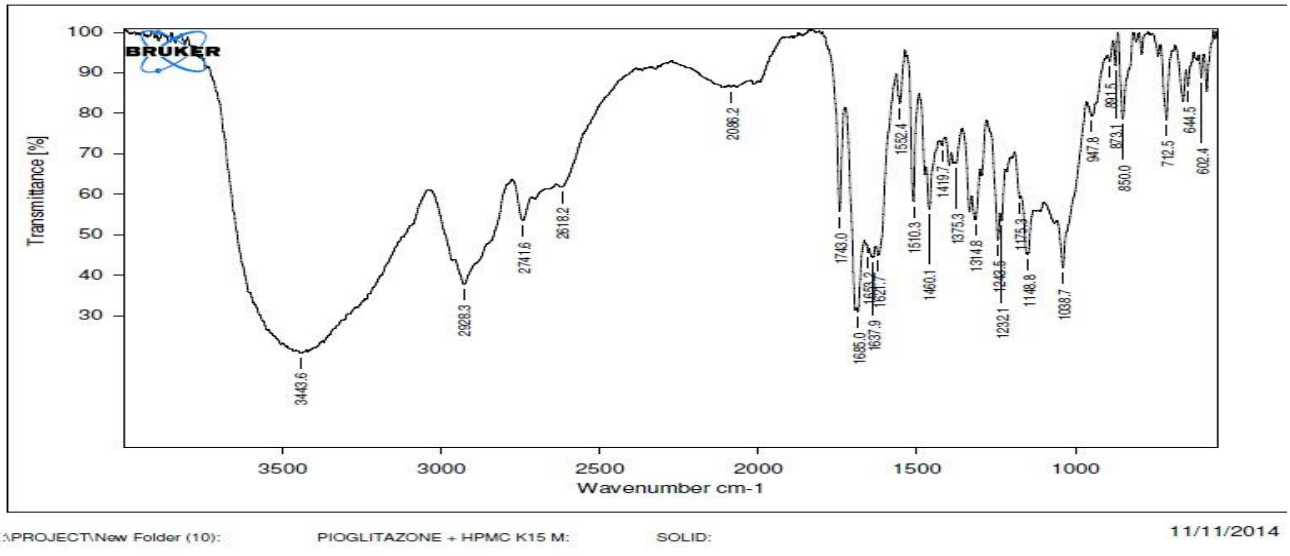
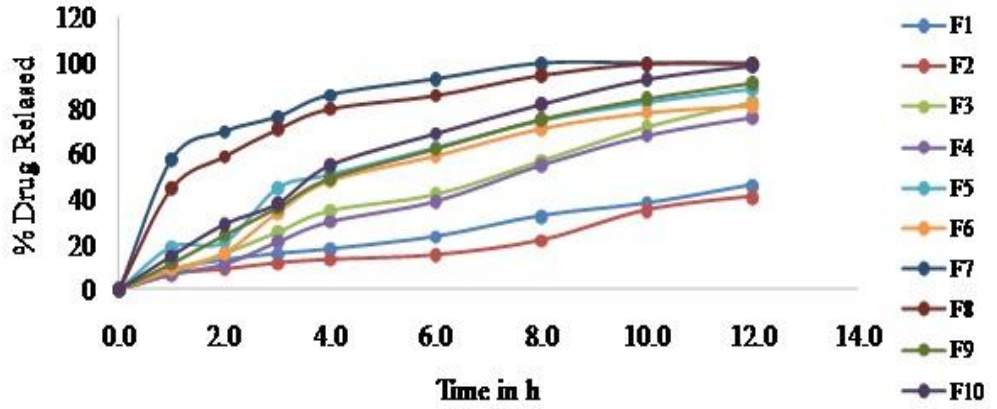


Figure 7. *In vitro* cumulative percentage release of Pioglitazone HCl from F1 to F10 tablets



DISCUSSION

The λ max of Pioglitazone in 0.1N HCl was scanned and found to have the maximum absorbance at 269 nm. Standard graph of Pioglitazone in 0.1N HCl was plotted by concentration range from 2 – 10 µg/ml and good correlation was obtained with R^2value 0.999; slope 0.046 and intercept 0.010. The formulations were prepared with HPMC K15M, HPMC K100M, Carbopol, PEO, Xanthan gum polymers and then evaluated.

The FTIR compatibility studies showed that there was no chemical change or interaction between drug and selected excipient which was evident by the replication of peaks in formulation spectra with that of pure drug indicate physical and chemical compatibility. The above excipients were selected and used for further formulation development. The angle of repose values obtained for the formulations of Xanthan gum, HPMC K15M are 31.96 ^{0}Ø, 35.3 ^{0} Ø. This indicates good flow property of the powder blend.

The compressibility index values for the formulations HPMC K15M and Xanthan gum are 19.6, and 17.3. This indicates the powder blend have good flow property and compression ability. The tablets size and thickness were also used to assess the quality of the tablet under uniform conditions of manufacturing process. Size of tablets ranged from 9.49 - 9.51 mm and thickness of the tablets ranged from 3.48±0.14mm. The total weight of each formulation was not maintained uniformly however the weight variation of the tablets within the limits of 5%. The measured hardness of tablets in all batches was ranged from 4.86±0.03kg/cm^2. Friability values were found to be less than 1% in all formulations and considered to be satisfactory. *In vitro* drug release profiles for all formulations were carried out and from the results obtained; it was observed that HPMC K100M 1:2 ratio and 1:3 ratios showed 41% release and 41% at end of 12 h. Whereas PEO 1:2 ratio and 1:3 ratios showed release about 86% and 76%. Carbopol 1:2 ratio and 1:3 ratios showed 89% and 81% drug release at end of the 12 h. Whereas Xanthan gum 1:2 ratio and 1:3 ratios showed 100% drug release at end of 8 h. HPMC K15M 1:2 ratio and 1:3 ratios showed 91% and 99% drug release at end of the 12 h. From the above results it was found that the release of drug from HPMC K15M gave the better release than other formulations. The kinetic order of release from the formulation was also studied. The results were indicated in table 5-6.

CONCLUSION

The analytical studies, absorbance maxima conforms the drug is pure and not degraded. The compatibility between drug and polymers were studied by using FTIR studies. The results depicts drug and polymer show no significant interaction between them. The evaluation results confirm that the prepared tablets have exhibited satisfactory physicochemical such as weight uniformity, thickness uniformity, friability, hardness and drug content uniformity.

From results of the drug content determination it was assured that there was uniform distribution of drug in the tablets and the deviations were within the acceptable limits. Release study of pioglitazone HCL tablets indicated the dug release from the formulations varies with different polymers. Among all the formulations F10 containing HPMC K15 showed better release of 99 % at 12 h. Based on the R^2 values it was confirmed that it follows higuchi model and follows first order. According to the peppas diffusion exponent of release profiles the ‘n’ values are below the 5 which indicates Fickian diffusion.

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