

Formulation, Development and Evaluation of Sustained Release Gastroretentive Floating Tablets of Antidiabetic Drug using Natural Polymers

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ABSTRACT

The major therapeutic goals in subjects with type 2 diabetes are to optimize blood glucose control, induce weight loss, and normalize lipid disturbances and elevated blood pressure. Pioglitazone HCl is a new class of compounds to improve insulin sensitivity in type 2 diabetes. formulation and in vitro evaluation of floating tablet of Pioglitazone HCl. For this purpose, HPMC K4, HPMC K15 and Gaur Gum were incorporated in the formulation and the effect of polymer concentration & viscosity on floating behavior and drug release kinetics was evaluated. In House floating tablet optimized formulation (F7) showed the release of drug from gastroretentive formulation 99.85% after 12 hrs. and marketed formulation showed the release of 98.85% after 1.5 hrs. When the regression coefficient values of were compared, it was observed that 'r²' values of first order was maximum i.e. 0.932 hence indicating drug release from formulations was found to follow zero order kinetics, which was sufficient for FGR tablets Pioglitazone HCl. Anomalous transport was confirmed from these tablets which corresponds to diffusion of water and swelling (polymer arrangement) mechanism or mixed order kinetics have an essential role in drug release. This result is encouraging, because a longer gastric residence time is an important condition for higher bioavailability of the drugs included in the FGR release dosage forms. Prepared floating tablets of Pioglitazone HCl may prove to be a potential candidate for safe and effective controlled drug delivery over an extended period of time for gastro retentive drug delivery system.

Keywords: Pioglitazone HCl, Gastro retentive, floating tablet, HPMC, Gaur Gum

INTRODUCTION

The oral route is considered as the most promising route of drug delivery. Drugs with narrow absorption window in the GIT have poor absorption¹. Therefore, GRDDS have been developed, which prolong gastric emptying time of drug and offers numerous advantages; improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment of small intestine². To formulate a successful stomach specific or gastroretentive

drug delivery system, several techniques are currently used such as HBS or floating drug delivery systems, low density systems, raft systems, incorporating alginate gels, bioadhesive or mucoadhesive systems, super porous hydrogels and magnetic systems. Swellable, floating and SR tablets are developed by using a combination of hydrophilic polymers (HPMC), natural polymers and effervescent substances (NaHCO_3 and citric acid) ¹ The major therapeutic goals in subjects with type 2 diabetes are to optimize blood glucose control, induce weight loss, and normalize lipid disturbances and elevated blood pressure³. Thiazolidinediones such as Pioglitazone HCl is a new class of compounds to improve insulin sensitivity in type 2 diabetes⁴. With an aim to improve the absorption and oral bioavailability we took an attempt to formulate floating drug delivery systems using Pioglitazone HCl as the drug candidate employing method of various grades like K4, K15 and natural polymers like guar gum.

MATERIALS AND METHODS

Material

Hydroxypropyl methylcellulose (HPMC K4M, HPMC K15M) was procured from Meditab Specialities Pvt. Ltd., Satara. Guar gum was purchased from S.D fine chemicals, Mumbai. Sodium bicarbonate, citric acid, magnesium stearate and talc were purchased from Mapromax, Life sciences Pvt. Ltd., Dehradun. Other solvents and chemicals used in the research were of LR grade. All the studies were carried in distilled water.

Method

Procedure for the determination of λ_{max}

Accurately weighed 10 mg of drug was dissolved in 10 ml of 0.1 N HCl solutions in 10 ml of volumetric flask. The resulted solution (1000 $\mu\text{g/ml}$) was used to prepare the concentration 10 $\mu\text{g/ml}$. The spectrum of this solution was recorded in 200-400 nm range using U.V. spectrophotometer (Labindia-3000+). After the complete scan λ_{max} of Pioglitazone HCl (figure 1) was found 222 nm.

Pre compression evaluation⁶

Flow properties and compressibility properties of powder mixture were evaluated by measurement of angle of repose, bulk density, tapped density, carr's index and hausner's ratio.

Angle of repose (θ)

The angle of repose was determined by using fixed funnel method. The physical mixtures of drug with different excipients were prepared and the accurately weighed drug powder or its physical mixture was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of

the funnel just touches the apex of the heap of the drug powder. The powder was allowed to flow through the funnel freely onto surface. The angle of repose was calculated using the following equation.

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

Where, h and r are the height and radius of the powder cone respectively.

Bulk density

Both loose bulk density (LBD) and tapped density (TBD) were determined were calculated using the following formulas.

$$\text{LBD} = \text{Powder weight/volume of the packing}$$

$$\text{TBD} = \text{Powder weight /tapped volume of the packing}$$

Compressibility index

The compressibility index of the granules was determined by Carr's compressibility index.

$$\text{Carr's index (\%)} = [(TBD - LBD)/TBD] \times 100.$$

Hausner's ratio

Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula⁹⁻¹¹.

$$\text{Hausner's ratio} = \text{Tapped density/Bulk density.}$$

Formulation development of tablets

Direct compression was followed to manufacture the gas generating floating tablets of Pioglitazone HCl. Nine different formulations (F1, F2, F3, F4, F5, F6, F7, F8, & F9) were prepared by direct compression [67]. All the polymers selected, drug and excipients were passed through sieve no. 40 before using into formulation. The amount and ratio of drug and polymers were weighed as per given in table 1 and all the formulation were used for further evaluations parameters⁷.

Table 1 Formulation composition of Pioglitazone HCl gastro retentive tablets

Excipients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Pioglitazone HCl	15	15	15	15	15	15	15	15	15
HPMC K 5	80	100	110	-	-	-	40	50	55
HPMC K 16	-	-	-	80	100	110	40	50	55
Gaur Gum	15	15	15	15	15	15	15	15	15
Citric acid	10	10	10	10	10	10	10	10	10
NaHCO₃	15	15	15	15	15	15	15	15	15
Mg(C₁₈H₃₅O₂)₂	5	5	5	5	5	5	5	5	5
Talc	10	10	10	10	10	10	10	10	10
Lactose	50	30	20	50	30	20	50	30	20
Total Weight	200	200	200	200	200	200	200	200	200

Evaluation of tablets⁸⁻¹⁰

All the tablets were evaluated for following different parameters which includes;

General Appearance

Five tablets from various batches were randomly selected and organoleptic properties such as color, odor, taste, shape, were evaluated. Appearance was judged visually. Very good (+++), good (++), fair (+) poor (-), very poor (- -).

Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach).

Friability

The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 100mg of drug was transferred to 100ml standard flask. The powder was dissolved in 50 ml of 0.1 N HCl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45 μ membrane filter. The filtered solution was diluted suitably and analyzed for drug content by UV spectrophotometer at a λ_{max} of 222 nm using of 0.1 N HCl as blank.

In vitro buoyancy studies

In vitro buoyancy was determined by floating lag time as per the method described by Rosa *et al*¹³. The tablets were separately in a 100 ml glass beaker containing simulated gastric fluid (SGF), pH 1.2 as per USP. The time necessary for the tablet to increase to the outside and float was determined as floating lag time. The experiments were conducted in triplicate. Total floating times were measured during *in vitro* dissolution studies.

Dissolution rate studies

In vitro drug release of the sample was done using USP-type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was set into the dissolution flask maintaining the temperature of 37 $\pm$ 0.5 $^{\circ}$ C and rpm of 75. One Betahistine hydrochloride tablet was set in every container of dissolution apparatus. The mechanical assembly was permitted to keep running for 10 hours. Sample measuring 5 ml were pulled back after each 1 hour up to 10 hours using 10ml pipette. The new disintegration medium (37 $^{\circ}$ C) was supplanted each time with a similar amount of the sample and takes the absorbance at 222nm using spectroscopy¹⁴⁻¹⁶.

Stability studies

The optimized formulation of Pioglitazone HCl were packed in strips of 0.04 mm thick aluminum foil laminated with poly vinyl chloride by strip packing and these packed formulations were stored in ICH certified stability chambers (Thermo labs, Mumbai) maintained at 40 $^{\circ}$ C and 75% RH for 6 months. The samples were withdrawn periodically and evaluated for their floating lag time, content uniformity and for *in vitro* drug release.

RESULTS AND DISCUSSION

Solubility of Pioglitazone HCl was soluble in distilled water, 0.1 N HCl and freely soluble in methanol. The melting point of Pioglitazone HCl was 182-185 $^{\circ}$ C and λ_{max} of Pioglitazone HCl was found to be 222 nm by using UV spectrophotometer (Labindia-3000+) in linearity range 5-25 μ g/ml Fig.1. Identification of drug was done by FTIR spectroscopy with respect to marker compound. It was identified from the result of IR spectrum as per specification. Tablet powder blend was subjected to various pre-formulation parameters Table 2. The angle of repose values indicates that the powder blend has good flow properties. The bulk density and tapped density of

all the formulations was found to be in the range of 0.335 to 0.362 (gm/ml) and 0.442 to 0.561 showing the powder has good flow properties. The compressibility index and hauser's ratio of all the formulations was found to be ranging between 19.91 to 39.93 and 1.249 to 1.665 which shows that the powder has good flow properties. Pioglitazone HCl tablet quality control tests such as weight variation, hardness and friability, thickness, drug content and drug release studies in different media were performed on the compression tablet. All the parameters such as weight variation, hardness, friability, thickness and drug content were found to be within limits Table 3.

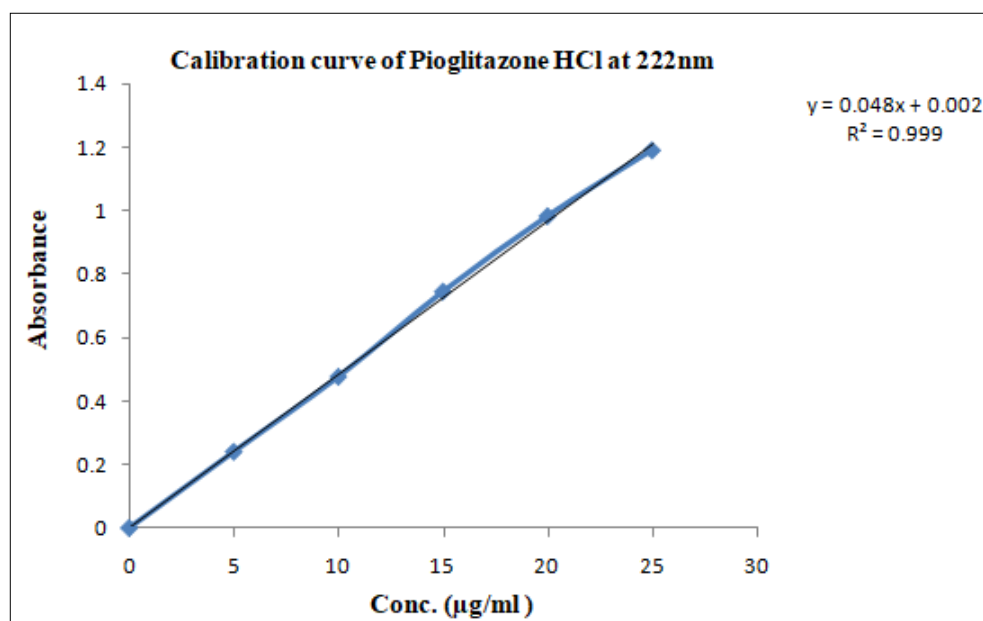


Fig. 1 Calibration curve of Pioglitazone HCl in 0.1 HCL at 228nm

Table 2 Result of pre-compression properties of Pioglitazone HCl GRF tablets

Material	Bulk density(gm/ml)	Tapped density(gm/ml)	Carr's index	Hauser's ratio
F1	0.354	0.442	19.91	1.249
F2	0.362	0.458	20.96	1.265
F3	0.358	0.457	21.66	1.277
F4	0.347	0.465	25.38	1.340
F5	0.335	0.462	27.49	1.379
F6	0.336	0.458	26.64	1.363
F7	0.338	0.452	25.22	1.337
F8	0.337	0.561	39.93	1.665
F9	0.338	0.547	38.21	1.618

Table 3 Results of post compression properties of Pioglitazone HCl GRF tablets

F. code	Thicknes* (mm)	Hardnes* (kg/cm ²)	Weight variation* (mg)	Friability* (%)	Drug content* (%)	Total floating duration* (h)	Floating lag times* (sec)
F1	3.2±1	4.8±0.2	200±4	0.785±0.12	98.85±0.65	MT 12	74±3
F2	3.4±2	4.8±0.1	205±3	0.658±0.14	97.96±0.32	MT 12	65±4
F3	3.5±4	4.7±0.2	203±5	0.745±0.23	98.95±0.47	MT 12	55±2
F4	3.4±5	4.7±0.2	204±4	0.799±0.41	98.85±0.85	MT 12	69±5
F5	3.5±2	4.8±0.3	200±2	0.805±0.25	99.12±0.42	MT 12	73±6
F6	3.6±3	4.8±0.4	207±1	0.882±0.36	98.85±0.21	MT 12	58±4
F7	3.4±4	4.7±0.3	198±7	0.874±0.21	99.45±0.56	MT 12	36±3
F8	3.4±3	4.9±0.2	204±5	0.785±0.41	98.85±0.12	MT 12	48±4
F9	3.5±4	4.7±0.2	203±6	0.812±0.42	98.74±0.78	MT 12	49±2

In the present study 9 formulations with variable concentration of polymers (HPMC K4, K 15 and Guar gum) were prepared by direct compression method and evaluated for physicochemical properties. The results of buoyancy lag time, total floating time and *in vitro* drug release was given in Table 3. The results indicated that optimizes formulation F8 on immersion in 0.1N HCl at 37±0.5°C tablets immediately and remain buoyant upto 12hr without disintegration. These 2 factors are essential for tablets to acquire density < 1, so that it remains buoyant on the gastric fluids. The *in vitro* drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, Higuchi's and Korsmeyer's models in order to determine the mechanism of drug release. In House Tablet optimized formulation (F7) showed the release of drug from gastroretentive formulation 99.85% after 12 hrs. and marketed formulation showed the release of 98.85% after 1.5 hrs. When the regression coefficient values were compared, it was observed that 'r²' values of first order was maximum i.e. 0.932 hence indicating drug release from formulations was found to follow zero order kinetics Table 4 Figure 4.

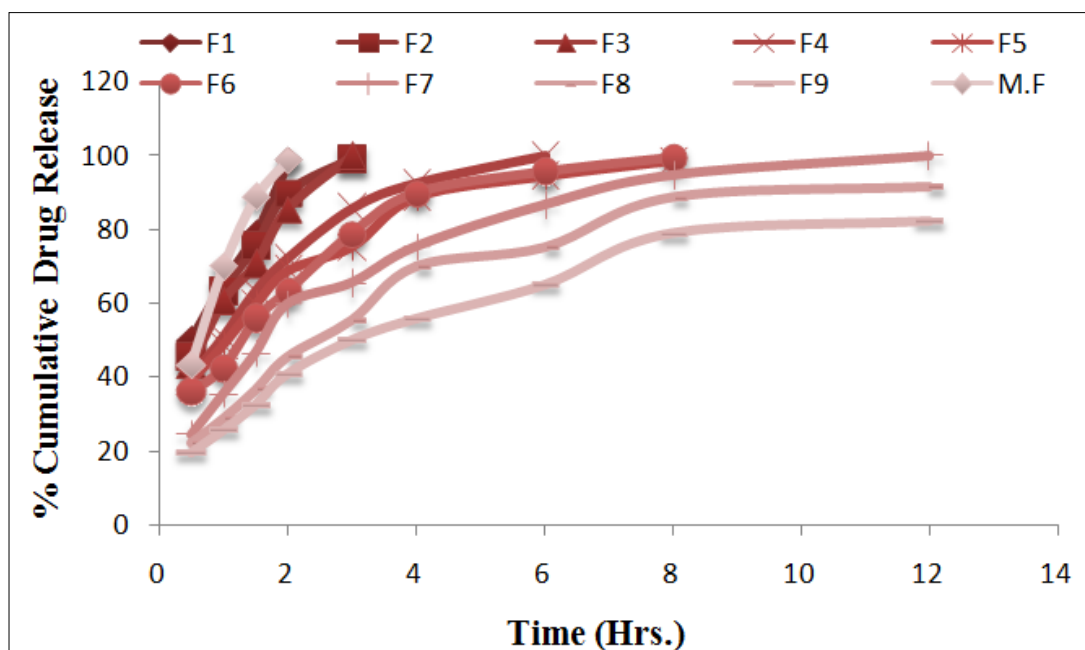


Fig.3 In-vitro drug release study of GRF tablets

Table 6 In-vitro drug release data for optimized formulation F8

Time (h)	Square Root of Time(h) ^{1/2}	Log Time	Cumulative* % Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	24.56	1.409	74.35	1.871
1	1	0	35.65	1.602	60.02	1.778
1.5	1.225	0.176	46.68	1.659	54.42	1.736
2	1.414	0.301	59.98	1.745	44.38	1.647
3	1.732	0.477	65.65	1.800	36.88	1.567
4	2	0.602	75.41	1.885	23.35	1.368
6	2.449	0.778	86.65	1.949	11.02	1.042
8	2.828	0.903	94.67	1.971	6.55	0.816
12	3.464	1.079	99.85	1.999	0.22	-0.658

Conclusion

This project work was based on formulation and in vitro evaluation of floating tablet of Pilglitazone HCl. For this purpose, HPMC K4, HPMC K15 and Gaur Gum were incorporated in the formulation and the effect of polymer concentration & viscosity on floating behavior and drug release kinetics was evaluated. In House floating tablet optimized formulation (F7) showed the release of drug form gastroretentive formulation 99.85% after 12 hrs. and marketed formulation

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