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Research Article

DESIGN AND EVALUATION OF PIOGLITAZONE HYDROCHLORIDE GASTRORETENTIVE FLOATING MATRIX TABLET

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ABSTRACT

Floating tablets of Pioglitazone hydrochloride were developed to prolong the gastric residence time, leading to an increase in drug bioavailability and reduced dose frequency. Three different grades of HPMC K 100M, K 15M, K 4M, MCC, sodium bicarbonate, magnesium stearate and talc were used as variant along with pioglitazone hydrochloride as active pharmaceutical ingredient. Sodium bicarbonate (16%) employed as gas generating agent for twelve formulations enable tablets to float. The tablets were prepared by wet granulation method. Tablets were evaluated for physical characteristics had shown that all of them comply with specifications of official pharmacopoeias. Pioglitazone hydrochloride release from prepared floating tablets (F7) was slow and spread over 24 h. These tablets exhibited a floating time of 48 h after a floating lag time less than180 sec. Drug release was diffusion controlled and followed zero-order kinetics. Non-Fickian diffusion was the drug release mechanism for all the tablets formulated. Results, FT-IR indicates that there is no chemical interaction between drug and polymer can be used to manufacture in tablet formulation.

Keywords: Floating drug delivery systems, Pioglitazone hydrochloride, Oral controlled release

INTRODUCTION

Floating drug delivery systems were first described by Davis in 1968[1]. It is possible to prolong the gastric residence time of drugs using these systems. Several techniques are used to design gastro retentive dosage forms. These include floating, swelling, inflation, adhesion, high-density systems and low density systems that increase the gastric residence time[2-3].gastric retention is useful for drugs which act locally; which have a narrow absorption window. various dosages forms developed for gastric retention include ,floating tablets[4],pellets[5],floating granules[6],floating microspheres[7-8]. Gastro retentive floating drug delivery systems (GRFDDS) which are retained in the stomach for longer period time. Pioglitazone hydrochloride is an effective oral anti-diabetic agent that belongs to the Thiazolidenones drug class and is wisely prescribed in management of non-insulin dependent (type-2) diabetes mellitus [9]. It is poorly soluble in aqueous fluids and is majorly absorbed from stomach [10]. Dosage forms that are retained in the stomach would increase its oral bioavailability and efficacy. Pioglitazone hydrochloride has a short biological half-life of 3-6 h and is eliminated rapidly [11]. Pioglitazone hydrochloride to be administered in 2 to 3 doses of 15 to 45 mg per day [12]. Therefore controlled release floating tablet formulations are needed for Pioglitazone hydrochloride to prolong its duration of action and to increase its oral bioavailability and reduced dosing frequency. In this investigation an attempt was made to design floating tablets of Pioglitazone hydrochloride using three different HPMC grades as polymers along with a gas generating agent.

MATERIALS AND METHODS

Materials

Pioglitazone hydrochloride drug was obtained as a gift sample from M/s Dr. Reddy's Laboratories, Hyderabad, India. Polymers HPMC K 100M, HPMC K 15M and HPMC K 4M, Methylcarboxycellulose, PVP K 30 were procured from Yarrow Chem. Products, Mumbai, India. Sodium bicarbonate was procured from Reachem Laboratory Chemicals Pvt. Ltd., Chennai, India. Magnesium stearate and talc I.P were procured from Molychem, Mumbai, India. All the chemicals were of analytical grade.

Drug-excipient compatibility studies

To study the compatibility of various formulation excipients with pioglitazone hydrochloride solid admixtures were prepared by mixing the drug with each formulation excipient separately in the ratio of 1:1 and stored in air tight containers at 30±2^{0}c/65±5%RH. The solid admixtures were characterized using Fourier transform infrared spectroscopy (FTIR, Bruker).The solid admixtures were characterized after three months.

Preparation of standard curve of Pioglitazone Hydrochloride

100 mg of pioglitazone hydrochloride pure drug was dissolved in 100 ml of 0.1 N HCl (stock solution-1000 µg/ml) and then placed in an sonicator for 10 min, from this 10 ml of solution was taken and the volume was adjusted to 100 ml with 0.1 N HCl (100 µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain the series of dilutions containing 2,4,6,8,10 µg/ml of pioglitazone hydrochloride solution. The absorbance of the above dilutions was measured at 269 nm by using the UV-Spectrophotometer using 0.1N HCl as the blank[13]. Then a graph was plotted by taking concentration on X-axis and absorbance on Y-axis which gives a straight line.

Preparation of Floating Tablets

Floating matrix tablets of Pioglitazone hydrochloride, each containing 30 mg were prepared by conventional wet granulation method employing three different grades of Hydrophillic polymer HPMC (K 100M , K 15M, K 4M) as shown in the formulae given in Table-1. A batch of 100 tablets was prepared in each case. A blend of Pioglitazone hydrochloride and the required quantities of HPMC, MCC used as an diluent and sodium bicarbonate used as an gas generating agent in the present formulations were granulated with solvent blend of water, methyl alcohol (1:1) and PVP K 30 (1%) is used as a binding agent. The wet masses were passed through 12 mesh sieve and the wet granules produced were dried at 60^{0}C for 1 h. The dried granules (16 mesh) after blending with talc (0.25 g) and magnesium stearate (0.25 g) in a laboratory cube blender for 5 min were compressed into 250 mg tablets of hardness 3.5-5.5 kg/sq.cm on a Elite Scientific & Equipments six station rotary tablet punch machine. The tablets were tested for hardness, thickness, friability and drug content.

Table1:Composition of pioglitazone hydrochloride floating tablet

Ingredients	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F11	F12
Pioglitazone hydrochloride	30	30	30	30	30	30	30	30	30	30	30	30
HPMC K-100M	55	-	-	110	-	-	130	-	-	150	-	-
HPMC K-15M	-	55	-	-	110	-	-	130	-	-	150	-
HPMC K-4M	-		55	-	-	110	-	-	130	-	-	150
Sodium bicarbonate	40	40	40	40	40	40	40	40	40	40	40	40
M.C.C	117.5	117.5	117.5	62.5	62.5	62.5	42.5	42.5	42.5	22.5	22.5	22.5
PVP K-30	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium sterate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

CHARACTERIZATION

Weight variation,thickness,hardness and friability determination

The weight variation of tablets were determined, thickness was measured using vernier calipers, friability was carried out on Roche friabilator (M/s. Elite Scientific & Equipments) and hardness was measured by using a Monsanto hardness tester[14-15].

Assay of pioglitazone hydrochloride

Twenty tablets were taken and powdered, powder equivalent to one tablet was taken and was allowed to dissolve in 100 ml of 0.1N hydrochloric acid by placing in a sonicator for 10 min. The solution was filtered, diluted suitably and analyzed using an UV-visible spectrophotometer at 269 nm.

Determination of swelling index

The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in 100 ml beaker of 0.1N HCl and after 1,2,4,6 and 8 h each beaker containing tablet was withdrawn, blotted with tissue paper to remove the excess water and weighed on the analytical balance. The experiment was performed in triplicate for each time point. Swelling index was calculated by using the following formula.

$$\text{Swelling index} = \frac{(\text{Wet weight of tablet} - \text{Dry weight of tablet})}{\text{Dry weight of tablet}} \times 100$$

In-vitro buoyancy studies

The *in vitro* buoyancy was determined by floating lag-time method. (As per the method described by Rosa et al[16]) The tablets were placed in a 100 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and the duration of the time the tablet constantly floats on the dissolution medium was noted as the Total Floating Time respectively (TFT).The experiments were conducted in triplicate.

In-vitro drug release studies

Release of Pioglitazone hydrochloride from the tablets was studied in 0.1N HCl (900 ml). A 8-station dissolution rate test apparatus (Model – DS 8000, M/s Lab India, India) was used. One tablet containing 30 mg of pioglitazone hydrochloride, at paddle speed of 50 rpm and a temperature of 37.5 ± 0.5^0C were employed in each test. Samples were (5ml) withdrawn at a time interval of 1hr and same volume of fresh medium was replaced and assayed spectrophotometrically at 269 nm using a Elico SL 159 UV-visible spectrophotometer[13]. Drug release experiments were conducted in triplicates.

Kinetic modeling of drug release

The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in the case of matrix systems. As a model-dependent approach, the dissolution data was fitted to popular release models such as zero-order, first-order, diffusion, Peppa's-Korsemeyer equations, Hixson Crowell[17-19] and Weibull equation models. The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from the matrix systems was studied by using Higuchi equation and Peppa's- Korsemeyer equation.

RESULTS AND DISCUSSION

Compatibility Study

The Infrared spectra of pioglitazone hydrochloride solid admixtures of drug and excipients were recorded between 500 to 3500cm^{-1} on FTIR. From the FTIR studies at 1693.6 and 1742.79 are the characteristics peaks of Pioglitazone Hydrochloride. No significant change occurred in the characteristics peaks of pioglitazone hydrochloride in all the solid admixtures. The spectrum shown in (Figures 1,2,3,4).

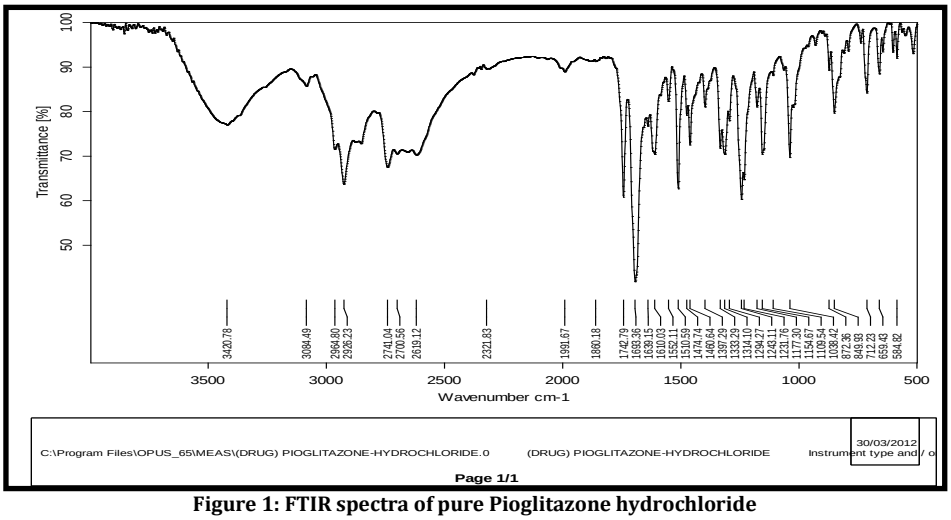

Figure 1: FTIR spectra of pure Pioglitazone hydrochloride

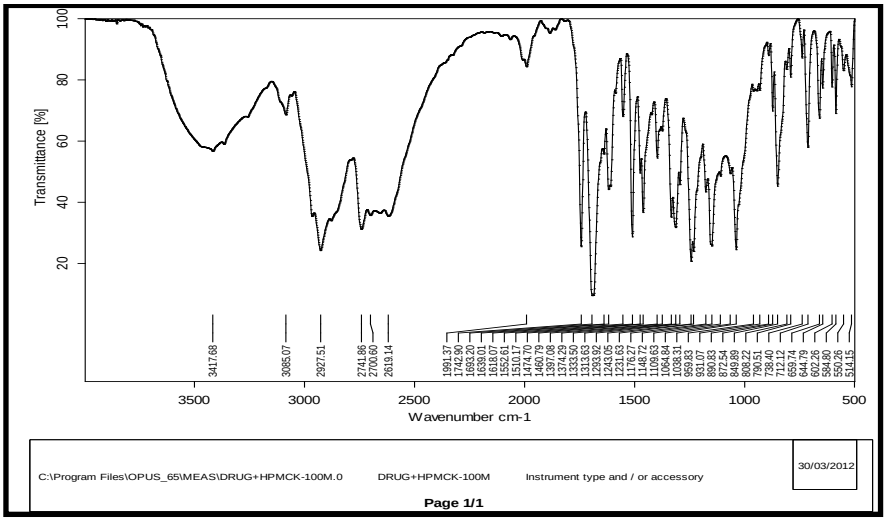

Figure 2: FTIR spectra of physical mixture of Pioglitazone hydrochloride with HPMC K100M

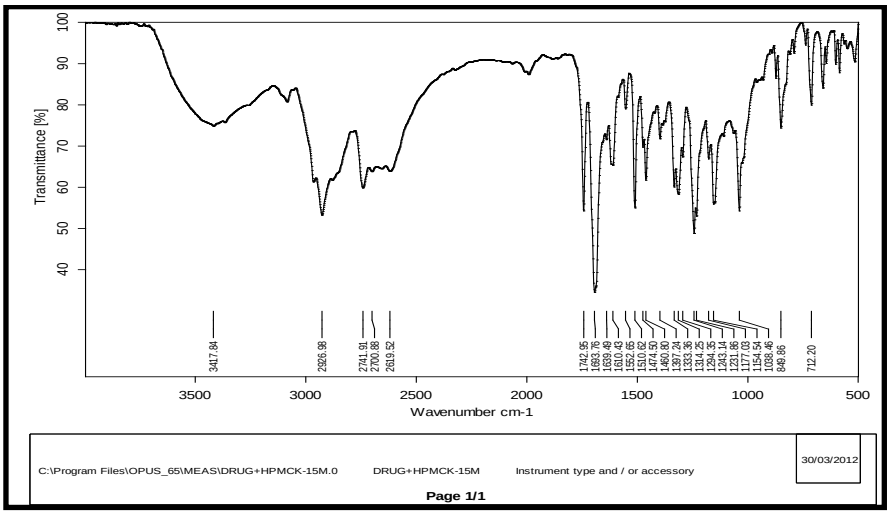

Figure 3: FTIR spectra of physical mixture of Pioglitazone hydrochloride with HPMC K15M

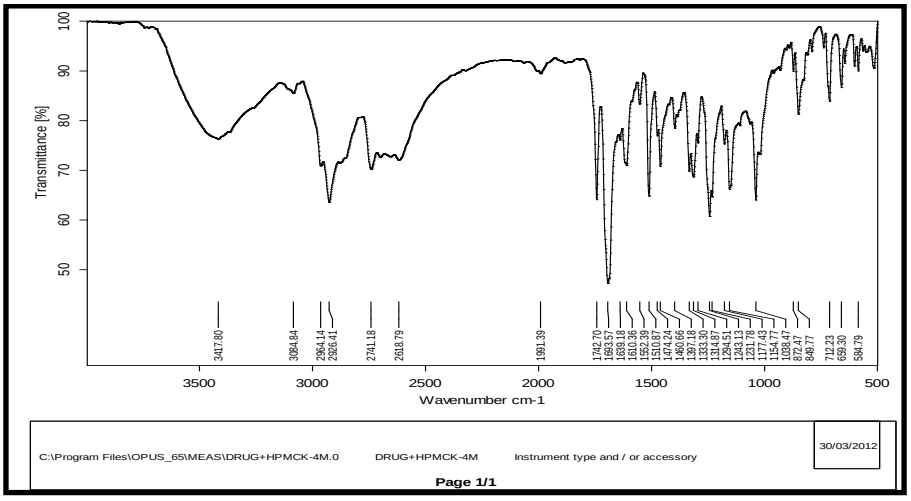

Figure 4: FTIR spectra of physical mixture of Pioglitazone hydrochloride with HPMC K4M

Physical properties of the compressed floating tablet systems

The hardness of all the formulations were in the range of 3.5-5.5 kg/sq.cm and Weight loss in the friability test was found to be in the range of 0.20%-0.40% this indicates sufficient hardness and has good mechanical resistance of tablets. Thickness and diameter of formulated tablets were of 4.02 mm and 8.0 mm respectively. The variations in weight were within the range of ±2.25 % complying with pharmacopoeial specifications (±7.5 %). The drug content varied between 96.13 to 101.01 % in all tablets with low standard deviation indicating content uniformity of the prepared batches. All the physical properties are with in the pharmacopoeial specifications and the above parameters are given in the table 2.

Table 2:Physicochemical parameters of the prepared formulations

Formulation	Uniformity Of weight (mg)	Thickness (mm)	Hardness (kg/cm²)	Friabilty (%)	Drug content (%)
F-1	251.0±1.98	4.02±0.10	4.0±0.866	0.20±0.07	97.06±4.24
F-2	249.65±2.25	4.02±0.07	5.0±0.288	0.28±0.16	96.53±2.12
F-3	251.55±1.90	4.01±0.03	5.5±1.322	0.40±0.15	101.1±1.41
F-4	250.0±1.68	4.02±0.04	4.5±0.288	0.28±0.19	96.43±5.65
F-5	250.4±1.40	4.02±0.03	5.0±0.501	0.20±0.05	98.06±4.64
F-6	250.0±1.98	4.01±0.10	4.5±0.577	0.26±0.08	98.67±1.46
F-7	251.0±1.46	4.02±0.06	4.0±0.290	0.24±0.11	96.24±6.36
F-8	250.2±1.88	4.04±0.04	4.0±0.288	0.20±0.02	97.06±5.51
F-9	251.0±1.60	4.02±0.09	4.5±0.765	0.40±0.15	98.24±2.18
F-10	250.2±2.20	4.02±0.05	3.5±0.500	0.20±0.04	95.52±5.16
F-11	249.8±1.00	4.01±0.04	4.0±0.763	0.26±0.06	96.61±4.94
F-12	250.5±1.91	4.02±0.06	5.0±0.288	0.24±0.07	96.13±4.02

Each data represents mean ± SD (n=3)

Buoyancy studies

All the formulations except F2, F3 and F6 remained buoyant for more than 24 h in 0.1N HCl medium with a lag time of below 180 sec. The F2,F3 and F6 were also buoyant for 15-20 h. The optimized concentration of sodium bicarbonate (16 %w/w) used as a gas generating agent. Due to the presence of the effervescent mixture in the tablets produced co_2 when it comes in contact with dissolution fluid. Due to the production of co_2 from the tablet matrix decreases the density of tablet below one making that tablets buoyant. The results are shown in the table 3.

Swelling Index

The swelling index of all the formulations given in the table 4 and graphically it is represented in Figure 5 & 6. The swelling behavior of all the formulations is due to formation of hydrogel by HPMC and swelling index also increases as the molecular weight and concentration of HPMC increases.The comparative swelling behavior of all the formulations with in 1 h is shown in figure 7.

Table 3:In vitro buoyancy study of twelve formulations

Formulation	Buoyancy lag time (sec's)	Total floatation Time (h)
F-1	55	24
F-2	38	20
F-3	26	15
F-4	98	44
F-5	69	38
F-6	45	20
F-7	122	48
F-8	94	40
F-9	72	25
F-10	180	>48
F-11	120	44
F-12	112	28

Table 4:Swelling index studies of pioglitazone hydrochloride floating tablets.

Time in (h)	F-1 (%)	F-2 (%)	F-3 (%)	F-4 (%)	F-5 (%)	F-6 (%)	F-7 (%)	F-8 (%)	F-9 (%)	F-10 (%)	F-11 (%)	F-12 (%)
1	49.2	34.4	24.0	58.4	46.8	39.8	62.2	51.6	43.0	66.4	55.6	46.4
2	63.0	44.64	31.6	69.0	52.0	42.4	74.4	62.4	48.4	79.6	68.2	55.6
4	87.2	80.35	46.8	95.4	85.0	63.6	98.8	90.4	72.6	103.2	96.4	86.0
6	103.6	92.2	62.0	108.0	98.4	86.8	120.2	108.2	96.4	129	112.6	103.8
8	110.6	101.3	80.0	124.1	112.6	99.6	136.4	121.4	107.6	147.6	128.6	119.6

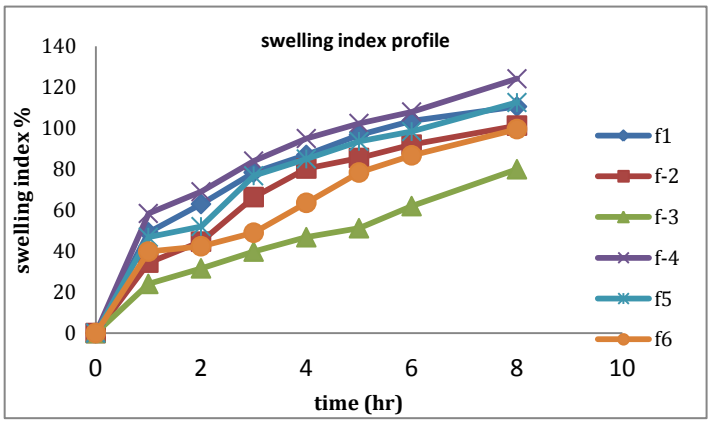

Figure 5: Swelling index of the different formulations (F1-F6)

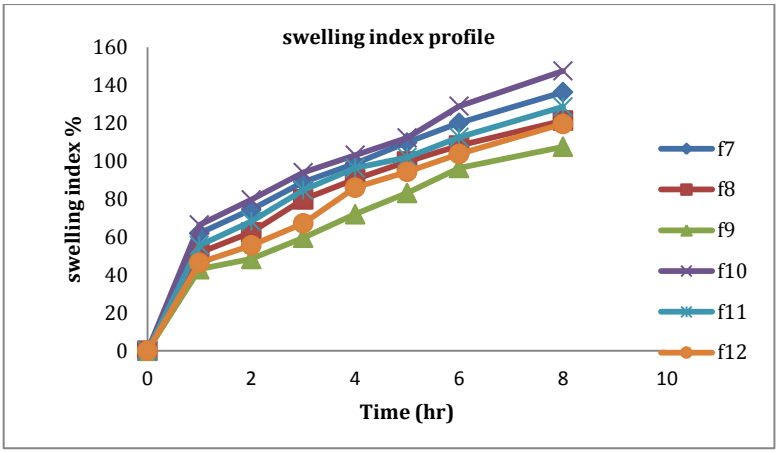

Figure 6: Swelling index of the different formulations (F7-F12)

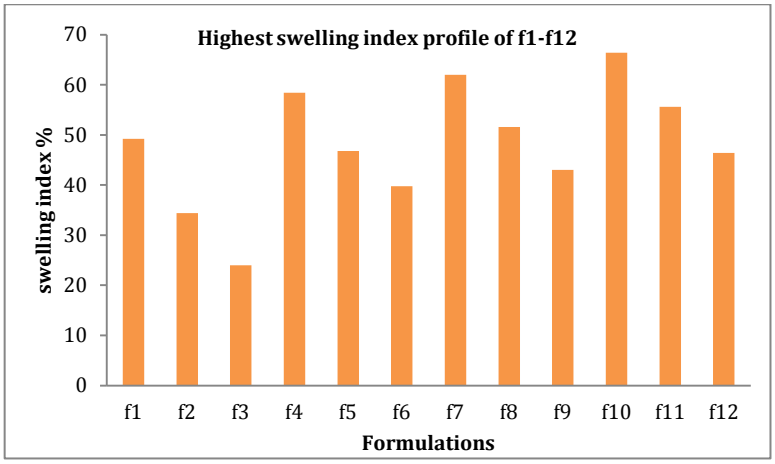

Figure 7: Highest swelling index of the floating tablets

***In-Vitro* Drug Release studies**

The results of the *in-vitro* drug release studies of Pioglitazone Hydrochloride floating tablets in 0.1N HCl shown in the table 5 and graphically shown in figure 8. All the trails performed with three tablets. In all the formulations the initial release for the first hour were varied between 5-18 % depending on HPMC grade and proportion. The release was found to be more controlled in the tablets with higher grade and higher proportions of the HPMC. The release of drug extended from 9 h to 15 h as the HPMC K 4M concentration varies from 22 % to 60 %. The release of drug extended from 12 h to 19 h as the HPMC K 15M concentration varies from 22% to 60%. The release of drug extended from 15h to 24 h as the HPMC K 100M concentration varies from 22 % to 60 %. The tablet formulation were found to swell in different extents forming a gel like structures during the drug release period depending up on the polymer proportions. The gel like structure recovered at the end of dissolution study. The 'n' values for all the formulations ranged from 0.754 to 0.931 indicating that the release mechanism was non-fickian. It can be inferred that the release was dependent on both drug diffusion and polymer relaxation. The value of 'n' increased as the concentration of polymer was increased except HPMC K 100M indicating that the influence of polymer relaxation on mechanism of drug release increased with polymer concentration.

Table-5. Cumulative drug release profiles of pioglitazone hydrochloride from floating tablets.

Formulation	Percentage Pioglitazone hydrochloride Released at Times (h) X ± S.D								T_{50} (hr)	Release rate (mg/hr)
	1.0	2.0	4.0	8.0	12.0	16.0	20.0	24.0		
F1	9.93 ± 1.52	18.26 ±1.08	28.8 ± 1.06	49.88 ± 1.58	79.75 ± 0.70	-	-	-	8.02	6.21
F2	13.13±1.93	22.21 ±2.25	38.85 ± 2.44	66.53 ± 3.15	94.21 ±2.53	-	-	-	5.84	7.85
F3	18.93±2.17	30.72 ±1.61	51.82 ± 1.53	88.78 ± 1.57	-	-	-	-	3.85	10.7
F4	7.24 ± 2.29	14.41 ±2.53	21.31 ±0.68	34.31 ±1.89	49.99 ± 2.83	66.13 ± 1.80	88.39 ± 2.95	-	12.0	4.24
F5	9.72 ± 1.75	17.74 ±2.35	30.03 ± 2.85	54.99 ± 2.12	74.45 ± 3.85	91.83 ± 1.53	-	-	7.27	5.54
F6	11.89±2.19	18.16 ±2.85	37.70 ± 0.92	66.51 ± 1.40	95.95 ± 2.09	-	-	-	6.24	7.99
F7	6.20 ± 0.73	11.41 ±2.12	20.17 ± 1.29	33.46 ± 1.79	43.57 ± 3.13	57.39 ± 1.13	72.68 ± 3.75	95.87 ± 2.73	14.2	3.99
F8	8.79 ± 1.85	13.91 ±3.08	24.10 ± 2.88	42.84 ± 1.30	59.79 ± 1.81	81.52 ± 1.04	-	-	9.22	5.01

F9	9.93 ± 1.46	16.19 ±2.69	30.25 ± 0.89	61.32 ± 1.18	88.38 ± 3.10	-	-	-	6.57	6.76
F10	5.06 ± 1.52	9.85 ±1.10	20.17 ± 2.14	34.73 ± 0.90	42.95 ± 1.37	57.39 ±1.53	72.68 ± 2.98	90.15 ± 2.37	14.4	3.79
F11	7.65 ± 0.95	11.83 ±1.50	18.18 ± 2.69	33.78 ± 1.34	48.97 ± 0.91	72.46 ± 2.50	-	-	12.2	4.91
F12	6.93 ± 2.17	15.96 ±1.43	31.27 ± 1.61	50.82 ± 1.53	82.55 ± 2.44	-	-	-	7.87	6.31

Each data represents mean ± SD (n=3)

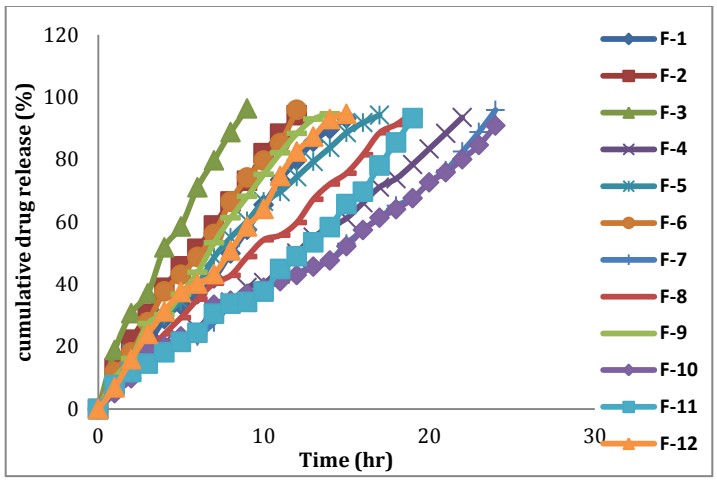

Figure 8: Dissolution profile of floating tablets (F1-F12) formulations.

Drug Release Kinetics

All the released data was fitted with different kinetic models like zero-order, first- order, Higuchi, Korsmeyer-Peppas, Hixson-crowell and Weibull equation models. The correlation coefficient values of all the kinetic models shown in the table 6. All the formulations in different kinetic models showed 'r' value greater than 0.9. Among all zero order kinetic model showed 'r' value nearer to one. This indicates the release of drug from Pioglitazone hydrochloride tablets follows zero order kinetics. This may be due to poorly soluble nature of pioglitazone hydrochloride. The drug release from the prepared pioglitazone hydrochloride floating tablets followed non-fickian zero order release.

Table 6: Data showing drug release kinetics for all the prepared formulations.

Formulation	Zero Order	First Order	Higuchi	Korsmeyer- Peppas	Hixson Crowell	Weibull	n
F-1	0.993	0.902	0.958	0.986	0.953	0.993	0.844
F-2	0.998	0.894	0.984	0.998	0.958	0.996	0.794
F-3	0.995	0.872	0.983	0.992	0.953	0.996	0.754
F-4	0.994	0.860	0.952	0.982	0.931	0.982	0.799
F-5	0.990	0.937	0.990	0.997	0.982	0.982	0.809
F-6	0.996	0.836	0.978	0.995	0.928	0.994	0.855
F-7	0.988	0.768	0.940	0.986	0.883	0.979	0.813
F-8	0.997	0.827	0.973	0.996	0.944	0.990	0.833
F-9	0.993	0.918	0.978	0.994	0.969	0.989	0.890
F-10	0.988	0.879	0.956	0.985	0.932	0.945	0.837
F-11	0.976	0.793	0.910	0.970	0.877	0.996	0.863
F-12	0.991	0.884	0.968	0.991	0.945	0.961	0.931

CONCLUSION

From the results, we conclude that floating drug delivery systems offer a suitable and practical approach to obtain controlled release of pioglitazone hydrochloride with enhanced bioavailability and reduced dosing frequency. HPMC K 100M is suitable polymer for once daily floating tablets comparable to HPMC K 15M and K 4M. Based on all the observations and results, it is revealed that the Pioglitazone hydrochloride floating tablets prepared by employing F7(HPMCK100M) was the best formulation. Results, FTIR indicated that there is no incompatibility, can be used to manufacture the tablet formulation with desired *in vitro* floating time and dissolution.

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