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Pioglitazone Hydrochloride Floating Tablets: Design, Evaluation and Release Kinetics

T Rama Rao[1], and Mohammed Asif Hussain[2]*

[1]Avanthi Institute of Pharmaceutical Sciences, Gunthapally (V), Hayathnagar- 501512, Ranga Reddy Dist, Andhra Pradesh, India.
[2]Blue Birds College of Pharmacy, Bheemaram, Hanamkonda-506015, Andhra Pradesh, India.
[3]Department of Pharmaceutics, Acharya Nagarjuna University, Nagarjuna Nagar, Guntur, 522510, Andhra Pradesh, India.

ABSTRACT

Pioglitazone hydrochloride is an oral antidiabetic drug used in the treatment of Type-II diabetes. It is soluble in acidic pH and absorption occurs only in proximal intestine. The objective of the present investigation was to formulate a Gastroretentive dosage form of Pioglitazone Hydrochloride to prolong the residence of drug in its absorption area. Buoyant tablets were formulated by direct compression method using different concentrations of (10%, 20% and 30% w/w) HPMC K15M as matrix former and sodium bicarbonate in the concentration of (10%, 15% and 20% w/w) as gas generating agent. The effect of variation in the concentration of polymer and sodium bicarbonate on drug release profile and floating properties were investigated. Formulations were evaluated for various physical parameters like hardness, thickness, weight variation, friability, buoyancy studies, *In-vitro* dissolution and percentage swelling studies. All formulations are within Pharmacopoeial specifications for physical parameters. An *In-vitro* buoyancy study reveals that all batches of formulations floats instantaneously. *In-vitro* dissolution studies reveal that increasing the polymer concentration led to retardation of drug release. Percentage swelling studies revealed that increasing the polymer concentration increased % swelling. The drug release of optimized formulation (F9) follows the Higuchi kinetic model, and the mechanism is found to be Fickian according to Korsmeyer-Peppas model (n value is 0.68). The similarity factor (f2) is found to be 59 for the optimized formulation. FTIR, DSC study reveals that there is no drug-excipient interaction.

Keywords: Pioglitazone Hydrochloride, Floating gastroretentive tablets, Release retarding polymers, Gas former, Sustained release.

Corresponding author

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INTRODUCTION

Quick and uncertain gastrointestinal transit may lead to incomplete release of the drug from the dosage form in the absorption zone leading to declined efficacy of the dose administered [1]. Gastroretentetive drug delivery systems (GRDDSs) can remain in the stomach region for quite a few hours and thereupon can considerably lengthen the gastric residence time of dosage form. Extended gastric retention enhances bioavailability, reduces drug waste augments solubility of drugs which are less soluble in alkaline pH [2]. Another important application of GRDDSs is the delivery of the drug locally in the stomach and small intestine [3]. Therefore several techniques designed to retain the dosage form in the stomach includes swelling devices [4], Bioadhesive devices [5], floating devices [6], high density systems [7]. The principle of floatable Preparation offers a simple and practical roadway to achieve increased gastric inhabitation time [8].

Pioglitazone Hydrochloride is used for the treatment of diabetes mellitus type II. Pioglitazone selectively stimulate the nuclear receptor peroxisome proliferator – activated receptor gamma (PPAR-γ) and to a lesser extent PPAR-α [9]. It is less soluble in aqueous fluids and is mainly absorbed from stomach [10]. Delivery systems that remain in the gastric region can enhance its bioavailability efficaciousness. Biological half life of Pioglitazone Hydrochloride is 3-6 hrs and is expelled quickly [11]. Pioglitazone Hydrochloride is administered in 2 to 3 doses of 1 to 45 mg per day [12].

In the perception of the above principles, a robust need was acknowledged for the development of a delivery system to deliver Pioglitazone Hydrochloride in the stomach and to enhance the efficiency of the drug providing prolonged action. In the present investigation we adapted an organized way in the production of Gastroretentive Pioglitazone Hydrochloride tablets.

MATERIALS AND METHODS

Materials

Pioglitazone Hydrochloride and HPMC-K15M were kindly provided by Lupin pharmaceuticals, Pune, India. Sodium bicarbonate, citric acid, talc, magnesium stearate were purchased from S.D. Fine chemicals Ltd. (Mumbai, India). Hydrochloric acid was obtained from Karnataka Labs. Pvt. Ltd. Barium sulfate (extra pure quality for x-ray diagnosis) was obtained from E.Merck (Darmstadt, Germany).

Methods

Preparation of Pioglitazone Maleate Floating Tablets

Tablets containing 30 mg Pioglitazone Hydrochloride were prepared, according to the design depicted in table 1 by direct compression. The respective powders, namely Pioglitazone Hydrochloride, release retarding polymer, a gas generating agent ($NaHCO_3$) were passed through sieve no.20 separately. Mixing of powders was carried out using a pestle & mortar for 10 min. then these powders and other ingredients viz. citric acid,

microcrystalline cellulose, were added in geometric proportions, and all these were mixed homogenously in a polybag for about 5-10 min then lubricated with the previously weighed and sieved magnesium stearate, talc to obtain the blend for compression. Finally, 300 mg of each mixture was weighed and filled manually into the die of sixteen station rotary tablet punching machine having 9 mm punches to produce the desired tablet. Detailed formulation is shown in table 1.

Table 1: Formulations of Floating Tablets of Pioglitazone Hydrochloride formulated employing HPMC-K15M

Formula code	Drug	HPMC K15M	Sodium Bicarbonate	Citric acid	Microcrystalline cellulose	Mg stearate	Talc
F1	30	30	30	10	194	3	3
F2	30	60	30	10	164	3	3
F3	30	90	30	10	134	3	3
F4	30	30	45	10	179	3	3
F5	30	60	45	10	149	3	3
F6	30	90	45	10	119	3	3
F7	30	30	60	10	164	3	3
F8	30	60	60	10	134	3	3
F9	30	90	60	10	104	3	3

Evaluation of Tablets [13]

The prepared tablets are evaluated for hardness using Pfizer hardness tester, friability was carried out on Roche friabilator, thickness was measured using Vernier calipers; weight variation was done by using electronic balance (shimadzu).

Tablet floating behavior [14].

The floating behavior of the tablets was visually determined, in triplicate, according to the floating lag time method described by Rosa et al. briefly, a tablet was placed in a glass beaker, containing 200ml of 0.1N HCl, maintained in a water bath at 37±0.5°C. The floating lag time “the time between tablet introduction & its buoyancy” and total floating duration “the time during which tablet remains buoyant” were recorded.

Determination of Drug Content [15]

Ten tablets with pre determined weight from each batch were taken and crushed in a mortar and weight equivalent to one average tablet was extracted in 100 ml of 0.1N HCl. The solution was filtered and the filtrate was sufficiently diluted and the absorbance was recorded against the blank at 250 nm. The drug content of the Standard containing the drug powder was also determined. The Drug content was determined by the formula.

$$\text{Drug content} = \frac{\text{Amount in test}}{\text{Amount in standard}} \times 100 \quad (1)$$

The tablet passes the requirements if the amount of the active ingredient in each of the 10 tested tablets lies within the range of 85% to 115% of the stated amount.

Determination of Swelling Index

Dimensional changes, weight gain or water uptake studies can be carried out to measure the swelling behavior of the formulations [16,17]. The swelling behavior of a dosage form was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in 200 ml beaker of 0.1N HCl (W1) placed in water bath at 37°±5°C. At regular intervals, the tablets were removed and the excess surface liquid was carefully removed by a filter paper. The swollen tablet was then reweighed (W2). The Swelling Index was calculated using the formula shown.

$$SI= (W2-W1)/W1 \quad (2)$$

***In vitro* Drug Release Studies** [18]

The release rate of Floating matrix tablets of Pioglitazone Hydrochloride was determined using USP Type 2 Apparatus. The dissolution test was performed in triplicate, using 900ml of 0.1 N HCl at 37± 0.5˚C at 50 rpm for 24 hrs. A 5ml sample was withdrawn from the dissolution apparatus at specified time points and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45-µm membrane filter and diluted if necessary. Absorbance of these solutions was measured at specified wave lengths described in developed analytical methods using Elico SL -159, UV-Visible Spectrophotometer. Cumulative drug release was calculated from the developed methods.
Drug Release Kinetics [13]

The drug release kinetics are studied by plotting the data obtained from the *in vitro* drug release studies in various kinetic models like zero-order, First order, Higuchi, Korsmeyer-Peppas model.

Zero order (eq.3) data is plotted as cumulative percentage drug released versus time.

$$C=K_0 t \quad (3)$$

Where C is the concentration, K_0 is the zero-order rate constant expressed as concentration /time, and t is time in hours.

First order (eq.4) is obtained by plotting log cumulative percentage drug released versus time.

$$Log C = Log C_0 - kt/2.303 \quad (4)$$

Where C_0 is the initial concentration of the drug, k is the first order rate constant, and t is the time.

As per Higuchi's (eq.5) data is plotted as cumulative percentage drug released versus square root of the time.

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$$Q=Kt^{1/2} \quad (5)$$

Where K is the constant of the system, and t is the time.

The mechanism of drug release is evaluated by plotting the percentage of drug released versus log time according to Korsmeyer-Peppas equation. Exponent n indicates the mechanism of drug release calculated through the slope of the straight line.

$$M_T/M\infty = Kt^n \quad (6)$$

Where $M_T/M\infty$ is the fractional solute release, t is the release time; K is a constant characteristic of the drug/polymer system. If the exponent n = 0.45 then the drug release follows the Fickian diffusion, and if 0.45 < n < 0.89, then it is said to be non-Fickian or anomalous release

RESULT AND DISCUSSION

The weight variations were within the range of ±7.5% complying with Pharmacopoeial specifications. Hardness of all the formulations was found to be between 4.52 to 5.60 kg/cm^2 and did not show any impact on the floating characteristics and the drug release. Thickness was between 4.20±0.05 to 4.50±0.02 which also falls under the Pharmacopoeial limits. The friability of all the formulations falls in the acceptable limits, i.e. below 1%. The drug content of all the tablets prepared was within 100 ± 5% of the labeled claim. All the Physical properties are within the Pharmacopoeial specifications and the above parameters result is given in the table 2.

Table 2: Physical properties of Gastroretentive tablets of Pioglitazone Hydrochloride formulated employing HPMC-K15M.

Formulations	Tablet weight (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Assay (%)
F1	301±1.75	5.56±0.658	4.29±0.12	0.15±0.02	101.75±0.50
F2	300±1.88	5.20±0.007	4.31±0.01	0.29±0.08	99.15±0.38
F3	298±2.60	4.52±0.610	4.28±0.15	0.50±0.18	98.50±0.85
F4	296±1.00	4.79±0.010	4.46±0.07	0.20±0.17	102.58±0.76
F5	302±2.50	4.65±0.055	4.40±0.05	0.30±0.15	100.52±0.15
F6	300±1.20	5.00±0.685	4.20±0.05	0.35±0.18	99.60±0.10
F7	297±3.65	5.34±0.175	4.43±0.06	0.42±0.35	98.45±1.60
F8	299±1.36	5.60±0.378	4.29±0.07	0.52±0.29	97.37±0.40
F9	298±2.16	4.56±0.054	4.50±0.02	0.26±0.10	100.75±0.13

All values are mean ± SD n=3.

In-vitro buoyancy determination

Floating drug delivery systems are intended to stay buoyant on the gastric fluid after a meal when stomach is full [13]. In the making of Pioglitazone tablets, the buoyancy was obtained by using sodium bicarbonate and citric acid as gas – developing salts into a swellable hydrophilic matrix. The comprehensive fabrication of this particular matrix is of swellable hydrophilic polymers. Imbibition of the dissolution medium into the matrix of tablet, leads to the interaction of fluid with effervescent base resulting in the formation and

entrapment of carbon dioxide gas within the swollen gel, thus causes buoyancy due to expansion of the matrix volume and decreased density. We observed that the amount of gas-generating effervescent base had a significant effect on the lag time of the system buoyancy (Table 3), as the percentage of sodium bicarbonate increases the floating lag time decreases. This phenomenon might be due to the generation of larger amounts of effervescence with higher sodium bicarbonate percentage. It was also observed that all formulations remain buoyant for more than 24 hr.

Table 3: *In vitro* Buoyancy and Total floating time of all formulations.

Formulations	Floating Lag Time (sec)	Total Floating Time (hrs)
F1	30	> 24
F2	20	>24
F3	12	>24
F4	47	>24
F5	38	>24
F6	27	>24
F7	66	>24
F8	55	>24
F9	42	>24

Swelling index

The swelling percentage obtained from water Imbibition studies of all the formulations is graphically represented in fig 1. We observed that swelling index increased with increase in the concentration of HPMC-K15M, and change in sodium bicarbonate concentration had little incremental effect on the swelling of the tablet. Result is shown in fig 1.

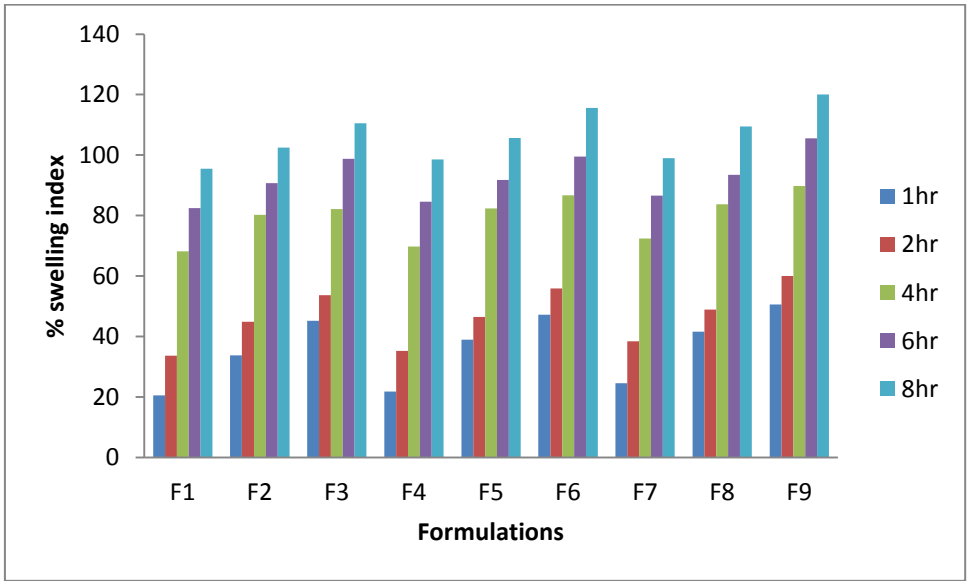

Fig 1: Influence of the polymer concentration on the swelling indices of Pioglitazone floating tablets at different time intervals.

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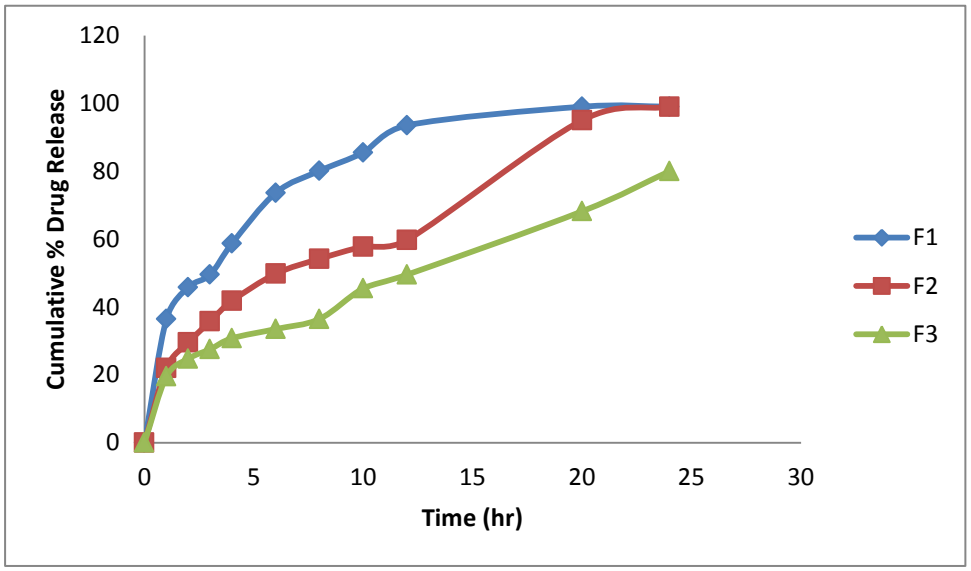
Drug release studies

In-Vitro drug release studies results of Pioglitazone hydrochloride floating tablets in gastric pH is shown in fig 2, 3 and 4 graphically. From the study it is clear that most of the formulations studied could control the rate of drug release for 24 hours. In all the formulations the initial release for the 1st hour was between 19 - 42% based on the concentration of HPMC – K15M. However, the release data of the drug relies on the type and concentration of the polymer, the formulation F1, F4 and F7 having the similar concentration of the polymer (10% w/w) but increasing concentration of (10%, 15%, and 20% w/w) sodium bicarbonate has shown 93.50%, 95% and 97.10% cumulative % drug release respectively at the end of 12hrs. Under alike experimental conditions, the cumulative % drug release of the formulation F2, F5 and F8 with 20 % w/w polymer concentration and 10%, 15 % and 20% w/w sodium bicarbonate concentration was 59.70%, 65% and 72.56% respectively at the end of 12hrs.

Figure 2: Release Profile of Pioglitazone Hydrochloride formulations F1, F2 and F3 prepared with HPMC-K15M.



Likewise F3, F6 and F9 formulations with 30% concentration of the polymer and increase in concentration of sodium bicarbonate as specified above exhibited summative % drug release of 49.50%, 56.45%, and 61.45% respectively at the end of 12 hrs. Drug release model clearly indicates that magnitude of delay of the drug release rate from the formulation (F1 – F9) was a role of polymer concentration. Based on the polymer concentration all the formulations (F1 – F9) inflated in diverse radius producing a gel like form during the drug release duration.

During the study it was observed that concentration of the gas – producing agents (10%, 15% and 20% w/w) has influenced on the drug release of the buoyant tablets in 0.1N HCl at 37°C ± 0.5°C as shown in fig 2, 3 and 4. During the investigation it was noticed that the concentration of the gas – producing agent and the drug release rate had a direct interrelation. Formulations (F7, F8 and F9) consisting the maximum gas – producing agent concentrations exhibited the maximal drug release rates of 97.10%, 72.56% and 61.45%, when compared to the other formulations having 10% and 15% concentration of sodium

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bicarbonate. The rise in concentration of gas – producing agent to 20% w/w might induce huge amounts of effervescence heading towards intensification in the degree of pore generation, hasty hydration of the tablets and thereupon showing a rapid drug release.

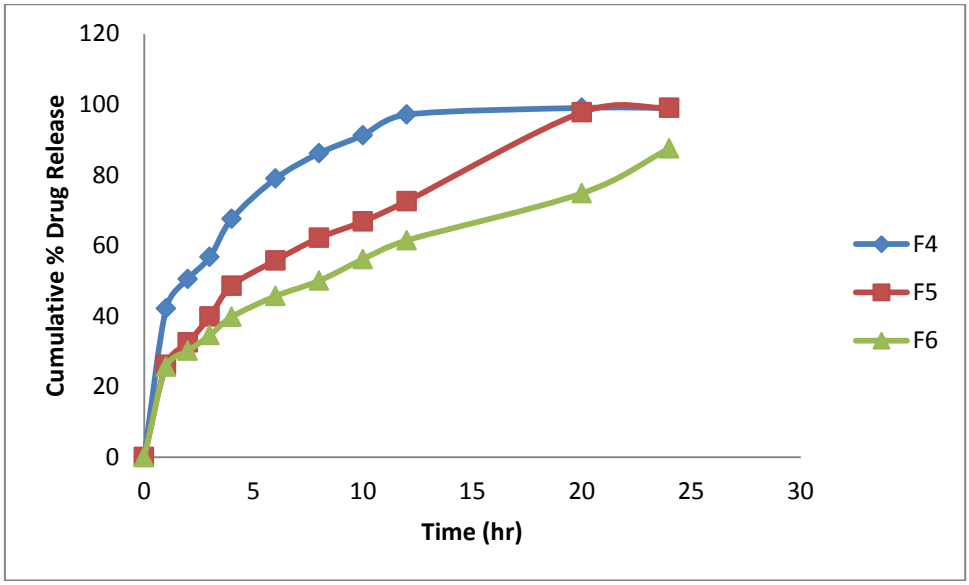

Figure 3: Release Profile of Pioglitazone Hydrochloride formulations F4, F5 and F6 prepared with HPMC-K15M.

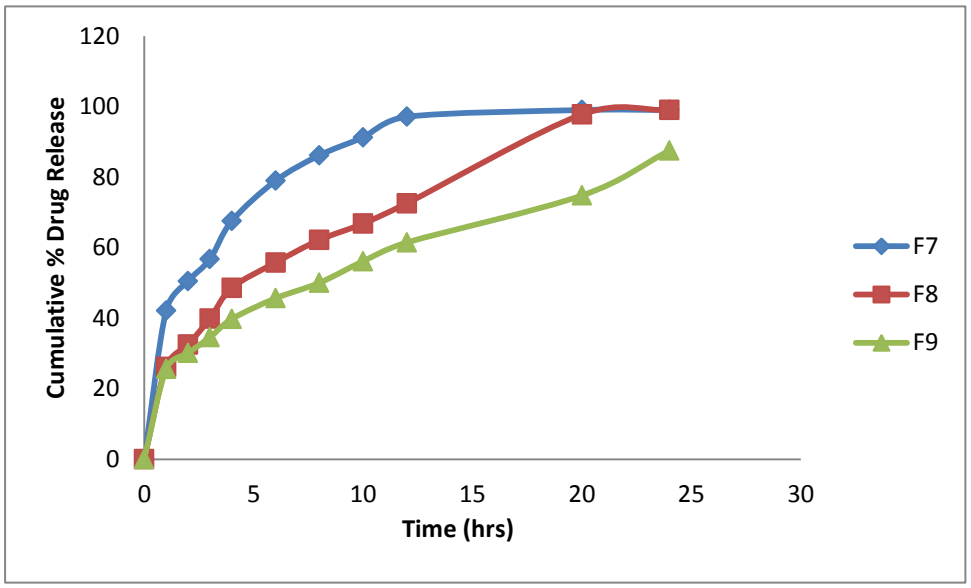

Figure 4: Release Profile of Pioglitazone Hydrochloride formulations F7, F8 and F9 prepared with HPMC-K15M.

The regression coefficient (R^2) values of release data of all formulations obtained by curve fitting method for zero order, first order, and higuchi model are reported in table 4. All the formulations follow the first order and Higuchi model. For the optimized formulation F9, the R^2 value of Higuchi 0.9879 (nearer to 1) is dominant than the other models which indicates the drug release depended on the square root of the time. (eq -5).

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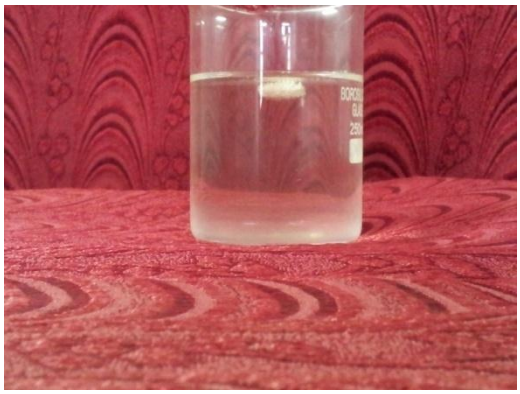
Table 4. Drug release kinetics for all the prepared formulations

Formulations	Zero order		First order		Peppas		Higuchi	Similarity factor
	R^2	K	R^2	K_1	R^2	n	R^2	(f2)
F1	0.7020	3.3028	0.9816	0.202	0.9665	0.3447	0.9193	30.295
F2	0.9229	3.5898	0.8900	0.168	0.9813	0.4642	0.9806	60.854
F3	0.9390	2.7684	0.9638	0.057	0.9517	0.4294	0.9733	49.620
F4	0.6588	3.1953	0.9794	0.201	0.9582	0.3229	0.8943	28.139
F5	0.9040	3.5596	0.9081	0.169	0.9908	0.4458	0.9901	54.111
F6	0.8995	2.8183	0.9540	0.064	0.9871	0.4101	0.9878	56.341
F7	0.6186	3.0866	0.9570	0.202	0.9492	0.2966	0.8678	26.305
F8	0.8774	3.5661	0.9375	0.183	0.9936	0.4339	0.9917	46.855
F9	0.8814	2.9022	0.9597	0.072	0.9856	0.3864	0.9879	59.002

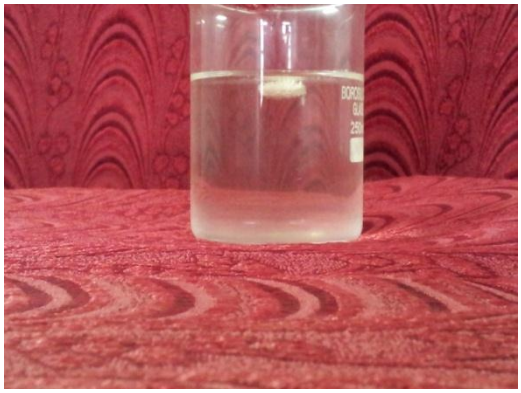
After 10 Seconds

After 14 Seconds



After 16 Seconds

After 1 Hour



After 24 Hours

Figure 4: Photographs taken during in vitro buoyancy study of formula F9 in 250ml 0.1 N HCl at different time intervals.

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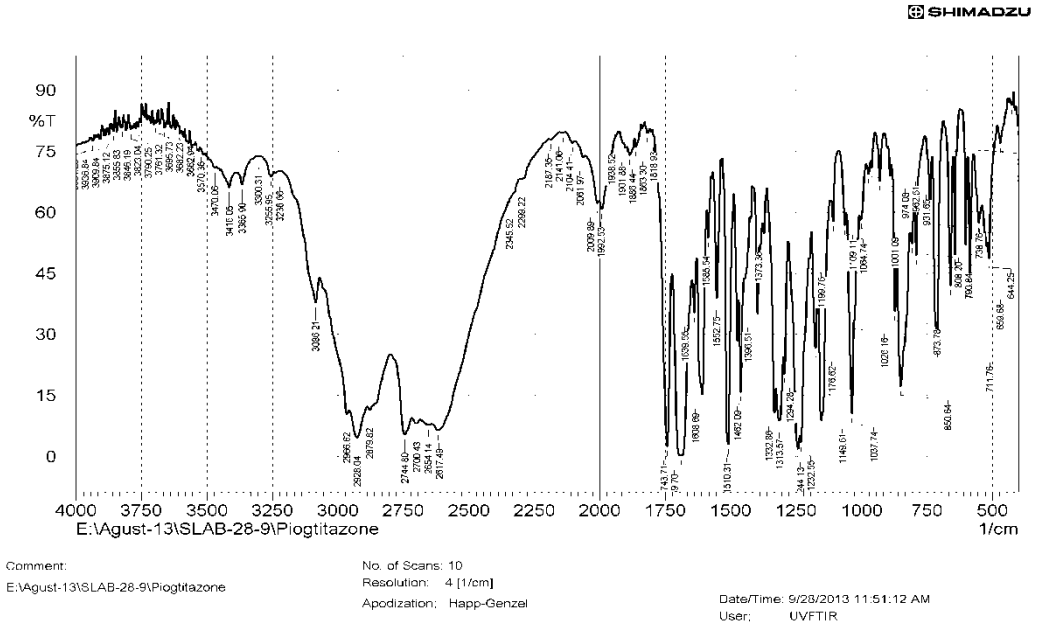

Fig 5: FTIR Spectra of pure Pioglitazone Hydrochloride

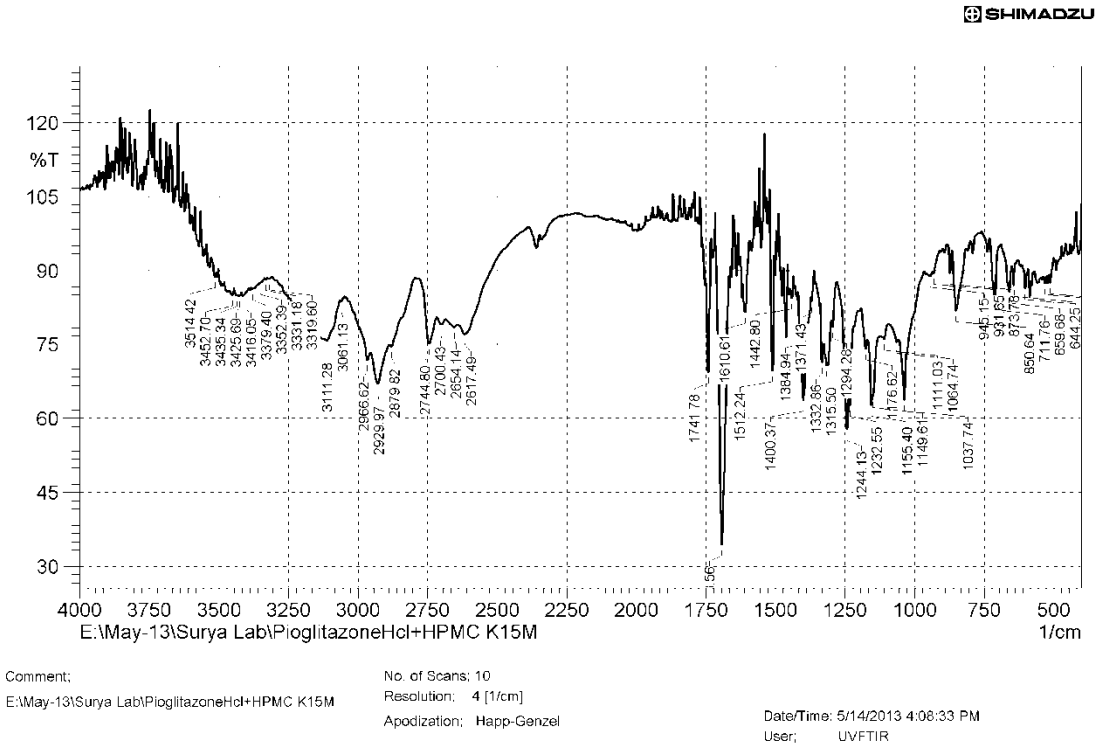

Fig 6: FTIR Spectra of Physical mixture of Pioglitazone Hydrochloride with HPMC K15M.

The mechanism of drug release is predicted by using Eq M_t / M∞ = Kt^n according to Korsmeyer – Peppas. The "n" value of optimized formulation F9 is 0.3864 and that of all formulations is between 0.2966 to 0.4490. This indicates that all the formulations follow the

Fickian type of diffusion. The similarity factor f2 value of optimized formulation F9 is found to be 59.002 which indicates sameness with theoretical drug release profile.

CONCLUSION

Assuring sustained release buoyant tablets of Pioglitazone HCl were triumphantly prepared by effervescent approach. Tablets comprising HPMC K15M (30% w/w) and (20% w/w) sodium bicarbonate (Optimized formula F9) exhibited acceptable results with respect to floating lag time, total buoyancy duration, swelling capacity and sustained drug release rates. The optimized formulation F9 follows the Higuchi Kinetic model and the mechanism of drug release is found to be Fickian. FTIR and DSC studies of pure Pioglitazone HCl and optimized formulation showed no interaction between drug and polymer.

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