Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 6, Issue 3, 2014

Original Article

DESIGN, DEVELOPMENT AND *IN-VITRO* EVALUATION OF INTRAGASTRIC BUOYANT TABLETS OF PIOGLITAZONE HYDROCHLORIDE

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Received: 22 Jan 2014, Revised and Accepted: 22 Apr 2014

ABSTRACT

Drugs that have narrow absorption window in the gastro-intestinal tract (GIT) will have poor absorption. For these drugs, gastro-retentive drug delivery systems offer the advantages in prolonging the gastric emptying time. Floating and sustained release tablets are developed by using a combination of hydrophilic polymer (Hydroxypropyl methylcellulose) and effervescent substance (Sodium bicarbonate and Citric acid) in different ratios. Percentage swelling, in vitro drug release, floating lag time and total duration of floating was conducted in 0.1N HCl (pH 1.2). The tablets showed acceptable physicochemical properties. The drug release of optimized formulation (F5) follows the Higuchi kinetic model, and the mechanism is found to be non-fickian according to Korsmeyer-Peppas ('n' value is 0.495). The similarity factor (f2) of formulation (F5) is found to be 74.66. Hence, formulation F5 was found to be optimized formulation out of all the floating matrix tablets of Pioglitazone Hydrochloride (F1-F9).

Keywords: Pioglitazone Hydrochloride, floating gastro-retentive tablets, release-retarding polymers, Gas formers.

INTRODUCTION

Drug delivery systems that can target drugs to a particular site in the body and can precisely control the drug release rates have paved a path in the development of novel drug delivery systems. Gastroretentive Drug Delivery Systems form an important part of such Advanced drug delivery system [1] Drug bioavailability of Pharmaceutical oral dosage forms is influenced by various factors. One important factor is the gastric residence time of these dosage forms. Conventional oral delivery systems have shown some limitations related to fast gastric emptying time [2] Floating drug delivery systems can overcome this problem by prolonging the gastric residence time of dosage forms. They remain buoyant in the stomach for prolonged period of time without affecting the gastric emptying rate of other contents [3]

Garg & Gupta classified the gastro-retentive dosage forms into four classes: (i) floating system (ii) expandable systems (iii) Bioadhesive systems and (iv) high density systems. Floating systems are of two types: (A) effervescent systems, depending on the generation of carbon dioxide gas upon contact with gastric fluids, & non-effervescent systems. The later systems can be further divided into four sub-types, including hydro-dynamically balanced systems; microporus compartment systems, alginate beads, & hollow microsphere microballons. In addition, super-porous hydrogels & magnetic systems were described [4, 5]. Floating Drug delivery systems are desirable for drugs (i) That are unstable in the intestinal or colonic environment, (ii) That are locally active in the stomach, and/or (iii) have low solubility in higher pH values [6].

Pioglitazone Hydrochloride is an effective oral anti-diabetic agent that belongs to thiazolidone diones drug class and is widely prescribed in the management of non-insulin dependent (Type-II) diabetes mellitus. It is poorly soluble in aqueous fluids and is majorly absorbed from stomach[7]. 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 hrs and is eliminated rapidly[8]. Therefore sustained release floating tablet formulations are needed for Pioglitazone to prolong its duration of action and to increase its oral bioavailability and to improve patient compliance. In the present study floating tablets of Pioglitazone Hydrochloride were designed employing HPMC-K100M as matrix former, sodium bicarbonate and citric acid as gas generating agents. The objective of the present investigation was the design and *in vitro* evaluation of more promising Pioglitazone Hydrochloride effervescent floating tablets based on release retarding gel-forming polymers like Hydroxypropyl methylcellulose (HPMC-K100M) in different concentrations with drug.

MATERIALS & METHODS

Materials

Pioglitazone Hydrochloride and HPMC-K100M 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).

Preparation of Pioglitazone Hydrochloride 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 (NaHCO3) 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, and then lubricated with the previously weighed and sieved magnesium stearate, talc to obtain the blend for compression. Finally, 300 mg of each mixture was compressed on sixteen station rotary tablet punching machine having 9 mm punches to produce the desired tablets

In-Vitro evaluation of the prepared tablets

Tablet weight variation [9]

Twenty tablets were randomly selected and accurately weighed, in grams on an analytical balance. Results are expressed as mean values ±SD.

Tablet thickness [9]: A Vernier calipers (for – bro engineers, Mumbai, India) was used to determine thickness of 10 randomly selected tablets. Results are expressed as mean values ±SD.

Drug content uniformity [9]: Ten tablets were individually weighed and crushed and quantity of powder equivalent to the mass

of one tablet (300 mg) was extracted in 100 ml of 0.1N HCl. The solution was filtered through a cellulose acetate membrane (0.45 µm).

The drug content was determined by UV spectroscopy (1601 – PC double beam spectrophotometer, Shimadzu, Kyoto, Japan) at a wavelength 250 nm after a suitable dilution with 0.1N HCl.

Table 1: Formulations of Floating Tablets of Pioglitazone Hydrochloride containing HPMC-K100M

Formula code	Drug	HPMC K100M	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

Tablet Friability [10]

According to the BP specifications 10 tablets were randomly selected and placed in the drum of a tablet friability test apparatus (Secor India scientific engg. Corp. Delhi, India). The drum was adjusted to rotate 100 times in 4 min. the tablets were removed, dedusted and accurately weighed. The percent weight loss was calculated.

Tablet swelling ability [11]

The swelling behavior of the tablets was determined in triplicate, according to the method described by Dorozynski et al. Briefly, a tablet was weighed (W1) and placed in a glass beaker, containing 200ml of 0.1N HCl, maintained in a water bath at 37 ± 0.5°C. At regular intervals, the tablets were removed & the excess surface liquid was carefully removed by a filter paper. The swollen tablet was then reweighed (W2). The swelling index [SI] was calculated using the formula (1).

SI= (W2-W1) / W1(1)

Tablet Floating behavior [12]

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.

Drug release studies [13]

Drug release studies of the prepared floating tablets were performed in triplicate, in a USP Dissolution Apparatus, type II (Paddle method) (Labindia Analytical instruments Pvt Ltd Delhi India) at 37±0.5°C. The paddles rotated at a speed of 100 rpm. The tablets were placed into 900 ml of 0.1N HCl solution (pH 1.2). Aliquots of 5ml were withdrawn from the dissolution apparatus at different time intervals & filtered through a cellulose acetate membrane (0.45µm). The drug content was determined spetrophotometrically at a wavelength of 250nm, as mentioned before. At each time of withdrawal, 5ml of fresh medium was replaced into dissolution flask.

Kinetic modeling of drug release profiles [14, 15]

The dissolution profiles of all formulae in 0.1N HCl were fitted to zero-order, first-order, Higuchi and Korsmeyer-peppas kinetic models. The model with the highest correlation coefficient was considered to be the best fitting one.

RESULT AND DISCUSSION

Table 2: Physicochemical Properties of Floating Tablets of Pioglitazone Hydrochloride containing HPMC-K100M

Formulation Code	Tablet weight (mg) Mean ± SD	Hardness (Kg/cm^2) Mean ± S.D	Thickness (mm) Mean ± SD	Friability (%) Mean ± SD	Assay (%) Mean ± SD
F1	303±2.32	4.62±0.165	4.30±0.01	0.30±0.18	98.23±0.34
F2	296±1.24	4.54±0.045	4.26±0.13	0.20±0.08	102.11±0.24
F3	287±3.74	5.00±0.126	4.29±0.02	0.50±0.06	99.12±1.32
F4	300±1.98	4.98±0.456	4.41±0.05	0.35±0.12	98.76±0.76
F5	293±4.89	5.00±0.658	4.31±0.05	0.29±0.15	101.76±0.84
F6	304±1.63	4.76±0.008	4.22±0.06	0.10±0.09	99.54±0.12
F7	292±2.78	5.01±0.154	4.28±0.10	0.27±0.01	97.34±0.35
F8	307±2.56	4.97±0.029	4.40±0.05	0.12±0.02	98.46±1.45
F9	296±4.46	4.56±0.367	4.43±0.05	0.20±0.18	101.56±0.35

All values are mean ± SD n=3

Physicochemical characteristics of tablets

All the formulations were tested for physicochemical parameters, like hardness, thickness, weight variation, friability and content uniformity. The results of the tests are shown in table 2. The weight variation was within the range of ±7.5% complying with Pharmacopoeial specifications. Hardness of the tablets was in between 4.54 – 5.01 kg / cm^2 and was maintained for all the batches in order to minimize the effect of hardness on the drug release because the effect of polymer concentration is the only area of interest. Tablet thickness was also used to assess the quality of tablets. Under uniform conditions of manufacture, the total weight of tablet and thickness were linearly related. The thickness of floating tablets ranged from 4.22 to 4.43 mm and linearly correlated with the weight of the tablets. The friability was below 1% for all the formulations which is an indication of good mechanical resistance of the tablet.

Drug content uniformity in all formulations was calculated and the percent of active ingredient ranged from 97.34% to 102.11% indicating good content uniformity.

The study indicated that all the prepared Formulations were good as the physicochemical parameters were found to be within the Pharmacopoeial limits.

Floating lag time and duration

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

Formulations	Floating Lag Time (sec)	Total Floating Time (hrs)
F1	36	> 24
F2	54	>24
F3	74	>24
F4	24	>24
F5	45	>24
F6	63	>24
F7	15	>24
F8	34	>24
F9	49	>24

The formulae F1, F2 and F3 contains $NaHCO_3$ ratio of 10% w/w and they have polymer (HPMC K 100M) ratio of 10%, 20% and 30% w/w respectively. In the study it was observed that F1 which had the least polymer(HPMC K100M) ratio had significantly shorter buoyancy lag time of 36 sec. whereas the formulae F2 & F3 containing 20% and 30% w/w of the polymer respectively, showed buoyancy lag times of 54 & 74 sec respectively. The F1 lag time was shorter than that observed with other formulae containing increasing concentrations of HPMC K100M (formulae F2 & F3). This could be explained with regard to the rate of the test medium penetration into these matrices and consequently the time required for gel formulation.

In the formulae F4, F5 and F6 the $NaHCO_3$ ratio maintained was 15% w/w and the release retarding polymer HPMC K100M was placed in the ratio of 10%, 20% and 30% respectively. In these formulations too it was observed that the formulae F4 containing the least amount of the polymer HPMC K100M has shown shorter buoyancy lag time of 24 secs, whereas the formulation F5 & F6 containing 20% and 30% w/w of the polymer respectively has shown buoyancy lag time in ascending fashion (45 and 63) i.e. as the polymer ratio increased the floating lag time also increased.

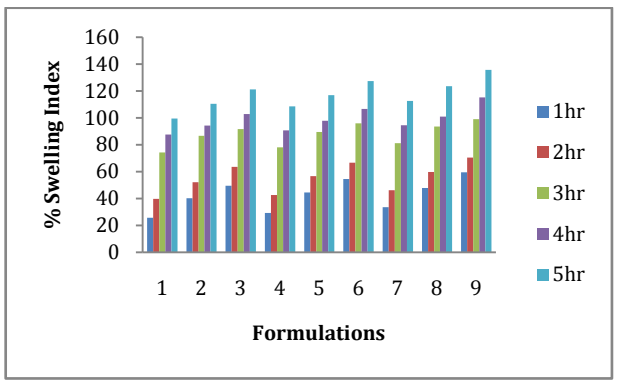

Fig. 1: Influence of the polymer concentration on the swelling indices of Pioglitazone floating tablets at different time intervals.

The formulae containing highest $NaHCO_3$ ratio of 20% w/w are F7, F8 and F9. Formula F7 had significantly shortest buoyancy lag time of 15 sec. Similar behavior was observed with the formulae F8 & F9 (34 & 49 sec) as that of the (F2, F3, F5 & F6) where polymer concentration was 20% & 30% w/w i.e. with increase in the concentration of the polymer the buoyancy lag time also increased.

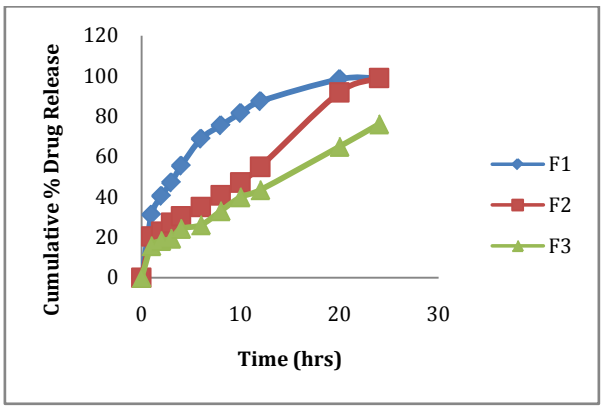

Fig. 2: Release Profile of Pioglitazone Hydrochloride formulations F1, F2 and F3 prepared from HPMC-K100M matrices

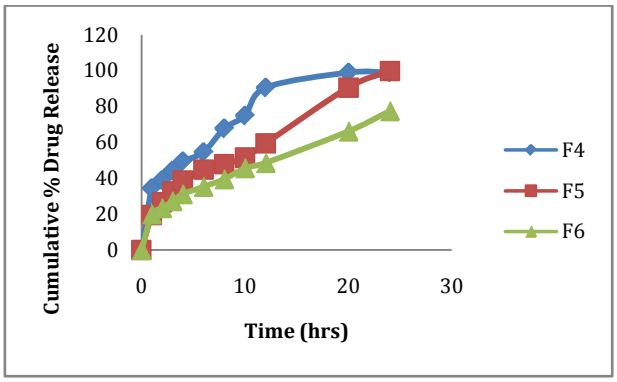

Fig. 3: Release Profile of Pioglitazone Hydrochloride formulations F4, F5 and F6 prepared from HPMC-K100M matrices.

Similar observations were noted by Gambhire et al [20] who concluded that as the percentage of $NaHCO_3$ increases, the floating lag time decreases. This phenomenon might be due to the generation of larger amounts of effervescence with higher $NaHCO_3$ percentage. This would lead to an increase in the rate of pore formation and consequently rapid hydration of the tablet matrices.

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-K100M, and change in sodium bicarbonate concentration had little incremental effect on the swelling of the tablet.

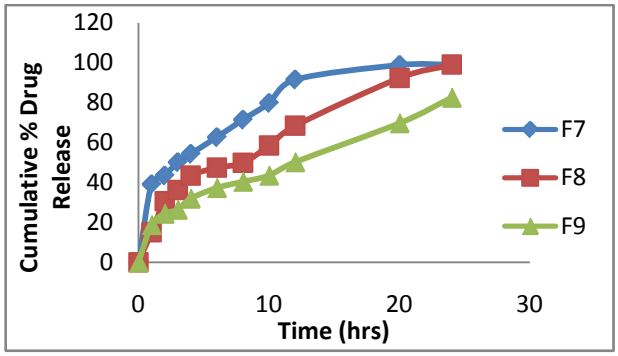

Fig. 4: Release Profile of Pioglitazone Hydrochloride formulations F7, F8 and F9 prepared from HPMC-K100M matrices

***In-Vitro* drug release studies**

Depending on the type and concentration of the investigated polymer in the current study, variable drug release profiles were successfully tailored. The influence of HPMC-K100M and sodium bicarbonate concentration on the release of Pioglitazone Hydrochloride from the floating tablets in 0.1N HCl (pH 1.2) at 37± 0.5 ^{0}C was shown in fig 2, 3 and 4. It is clear that the formulae prepared succeeded in controlling the rate of drug release for 24 hr. However, the drug release rate was dependent on the type and concentration of the investigated polymer the formulae F1, F4 and F7 having the same polymer concentration (10 % w/w) but increasing concentration of 10%, 15% and 20% w/w $NaHCO_3$ has shown 87.30%, 90.53% and 91.5% cumulative % drug release respectively at the end of 12hrs. Under identical experimental conditions, the cumulative % drug release of formulae F2, F5 and F8 with 20% w/w polymer concentration and 10%, 15% & 20% w/w $NaHCO_3$ concentration was 54.96%, 59.40% & 68.40% respectively at the end of 12hrs.

Similarly F3, F6 and F9 formulae with 30% polymer concentration & incremental concentration of $NaHCO_3$ as mentioned above showed cumulative % drug release of 43.50%, 48.60% and 50.20% respectively at the end of 12hrs. From the pattern of the drug release it is clear that the degree of retardation of the drug release rate from the formulae F1 to F9 was a function of polymer concentration. The higher viscosity of HPMC-K100M would promote the formation of highly viscous gels upon contact with aqueous fluids. This would promote retardation of the drug release rate. In a parallel line, Siepmann & Peppas[21] suggested that the drug release from HPMC matrices is sequentially governed as follows:

(i) At the beginning, steep water concentration gradients are formed at the polymer / water interface resulting in water imbibitions into the matrix.

(ii) Due to the imbibitions of water, HPMC swells resulting in dramatic changes of polymer and drug concentrations and increasing dimensions of the system.

(iii) Upon contact with water, the drug dissolves and diffuses out of the device due to concentration gradients.

(iv) With increasing water content, the diffusion coefficient of the drug increases substantially.

It is worth to note that, a burst effect was observed with all formulations. This could be due to the fact that the gel layer, which controls the drug release rate, needs some time to become effective. The rapid drug dissolution from the surface of the tablets could be another possible explanation. Interestingly, this effect was less predominant with those formulas containing higher HPMC-K100M ratio; F3, F6 and F9.

Kulkarni and Bhatia[22] suggested that the resulting gel-like networks surrounding these matrices, upon contact with aqueous media, would produce strong surface barriers that would effectively reduce the burst drug release.

The influence of the gas-forming agent concentration (10%, 15% & 20% w/w) on the release of the drug from the floating tablets in 0.1N HCl (pH 1.2) at 37±0.5 ^{0}C was shown in fig 2, 3 and 4. A direct relationship was observed between the investigated concentration of the gas-forming agent and the drug release rate, formulae (F7, F8 & F9) containing the highest gas-forming agent concentrations showed the highest drug release rates 91.5%, 68.4% & 50.20%. When compared to formulations F1 to F6 at the end of 12 hrs. The elevation of the gas-forming agent concentration to 20% (w/w) would generate large amounts of effervescence leading to an increase in the rate of pore formation, rapid hydration of the tablets matrices and consequently a faster drug release rate.

Table: 4. Kinetics of all Formulations containing HPMC K100M

Formulations	Zero Order		First Order		Peppas		Higuchi	Similarity Factor
	R^2	K	R^2	K_1	R^2	N	R^2	
F1	0.7559	3.4164	0.9878	0.192	0.9809	0.3854	0.9503	33.85
F2	0.9722	3.7611	0.8453	0.162	0.9276	0.5149	0.9413	**67.56**
F3	0.9730	2.8008	0.9721	0.053	0.9388	0.5112	0.9601	41.46
F4	0.8157	3.5212	0.9600	0.202	0.9623	0.3765	0.9629	38.20
F5	0.9494	3.6296	0.7755	0.191	0.9776	0.4959	0.9776	**74.66**
F6	0.9285	2.6616	0.9712	0.053	0.9715	0.4244	0.9851	47.84
F7	0.7634	3.3289	0.9727	0.197	0.9727	0.3310	0.9468	34.02
F8	0.9199	3.6586	0.8864	0.162	0.9635	0.5352	0.9687	**59.13**
F9	0.9404	2.8605	0.9577	0.062	0.9708	0.4495	0.9783	**51.43**

The *in vitro* drug release data from all the matrix formulations of Pioglitazone Hydrochloride were fitted to Zero order, First order, Higuchi and Korsmeyer-Peppas models. Most of the formulations followed First order kinetics (Table 4). To evaluate the drug release mechanism from the matrix tablets, plots of percent drug released vs square root of time as per Higuchi's equation were constructed. These plots were found to be linear with all the formulations (R^2 = 0.9413 to 0.9851) indicating that the drug release from the tablets was diffusion controlled.

The drug release from the polymeric systems is mostly by diffusion and is best described by fickian diffusion. But in case of the formulae containing swelling polymers, as HPMC K100M, other processes take place, like relaxation of polymer chains, imbibitions of water causing polymers swelling and considerable volume expansion.[9] Korsmeyer and Peppas equation[15] superposes two apparently independent mechanisms of drug transport, Fickian diffusion and a case-II transport, for the description of drug release from a swelling polymer. For a matrix tablet when 'n' takes the value of 0.45 it indicates diffusion-controlled drug release. Values of 'n' between 0.45 and 0.89 can be regarded as an indicator for both the phenomenon (anomalous transport).

To confirm the exact mechanism of drug release, the data were fitted to Korsmeyer-Peppas equation. The values of 'n' with the corresponding correlation coefficients for all the formulae are shown in table 4. Formulation F1, F4, F6 & F7 has shown the 'n' value less than 0.45 indicating the drug release by fickian diffusion whereas the remaining formulations F2, F3, F5, F8 & F9 have 'n' values between 0.45 and 0.89, indicating anomalous transport. The relative complexity of these formulae may indicate that the drug release is controlled by more than one process, a coupling of diffusion and erosion.

To compare *in vitro* drug release profiles of all the matrix formulations with the theoretical release profile, similarity factor (f2) analysis was carried out. The f2 values of the formulations F2, F5, F8 & F9 were found to be greater than 50 indicating that the drug release behavior of these formulations was similar to the theoretical release profile. Among all the matrix formulations, F5 was found to be the best one based on its highest f2 value.

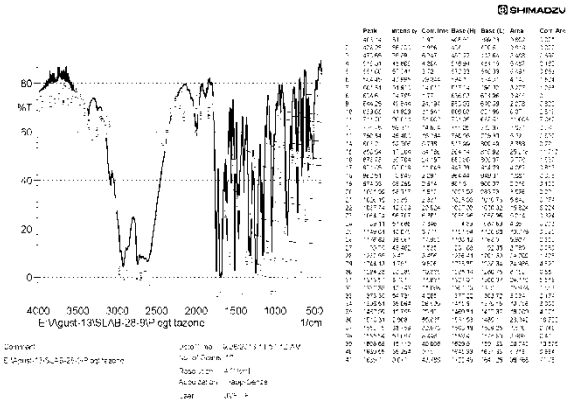

Fig. 5: FTIR spectra of pure Pioglitazone Hydrochloride

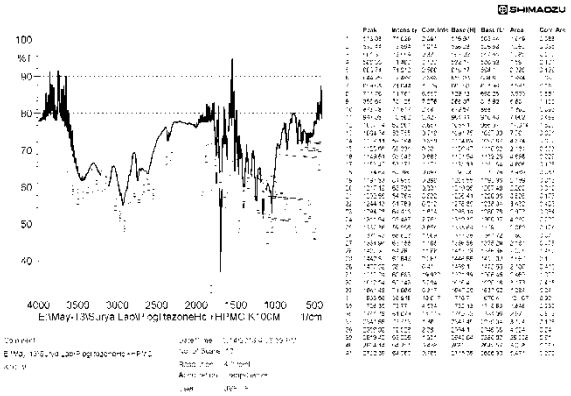

Fig. 6: FTIR spectra of physical mixture of Pioglitazone Hydrochloride with HPMC K100M

Compatibility studies

The Infrared spectra of Pioglitazone hydrochloride solid admixtures of drug excipients were recorded between 500 to 4000 cm^{-1} on FTIR. The Peaks obtained in the spectrum of formulation correlated with the peak of drug spectrum and there were no significant extra peaks. This indicates that the drug was compatible with formulation components. The spectra of pure drug and optimized formulation were shown in Fig. 5 and 6.

Fig. 7: A photograph taken during the in vitro dissolution study of formula (F6) in a USP TYPE II apparatus.

CONCLUSION

Assuring sustained release floating tablets of Pioglitazone HCl were successfully prepared by effervescent approach. Tablets comprising HPMC K100M (20% w/w) and (15% w/w) sodium bicarbonate (Optimized formula F5) exhibited acceptable results with respect to floating lag time, total buoyancy duration, swelling capacity and sustained drug release rates. The optimized formulation F5 follows the Higuchi Kinetic model and the mechanism of drug release is found to be non-fickian. Results, FTIR studies of optimized formulation indicated that there is no incompatibility of pure Pioglitazone HCl and polymer.

ACKNOWLEDGEMENT

The authors are thankful to Blue Birds college of Pharmacy for providing us the facilities to carry out the research work.

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