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Formulation and Evaluation of Floating Matrix Tablets of Pioglitazone Hydrochloride delivery

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Abstarct

Objectives: The objective of the present study was development and evaluation of effervescent floating matrix tablets of pioglitazone hydrochloride for maintenance of steady state plasma concentration up to 12 h.

Materials and Methods: Tablets were prepared by wet granulation method using different grades of HPMC (K4M/K15M/K100M/ Metalose 90 SH) and PEO (WSR301/WSR coagulant) in 10%, 15% and 20% concentrations. Formulations were evaluated for various physicochemical parameters. Drug and excipients interaction analyzed by FTIR and DSC studies. *In-vitro* buoyancy studies, drug release and water up take studies were performed in 1.2 pH hydrochloric acid as dissolution medium for a period of 12 hrs. *X*-ray studies were conducted on optimized formulation.

Results: Physicochemical parameters of prepared matrix tablets are with-in-house specifications. All batches of HPMC grades floats instantaneously and total floating time is 12 hrs or more than 12 hrs (except F1&F2) but PEO grades total floating time is 9 h and drug releases up to 12 h. All the formulations were fitted into higuchi model and release mechanism was non-Fickian (anomalous) diffusion mechanism. Optimized formulation F3 (HPMC K15M 20%) showed 7.1 ± 0.2 h of buoyancy in the stomach.

Conclusion: It has been concluded that HPMC K15M 20% is sufficient to prepare oral floating matrix tablets of pioglitazone.

Keywords

Polyethylene Oxide; Gastroretentive; Pioglitazone Hydrochloride; Sustained Release; Floatation; In-Vitro Dissolution

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Introduction

The oral route is most convenient and commonly used method due to ease of administration, improved patient compliance, ease of manufacturing and high degree of flexibility in dosage forms. Bioavailability is limited in conventional dosage forms due to its short gastric residence time (GRT) and narrow absorption window in small intestine. Short gastric emptying time leads to incomplete release of the drug and reduced efficacy of administered drug. To overcome this restriction and to increase the bioavailability of drugs several controlled drug delivery systems with prolonged gastric residence times reported recently [1, 2].

The main approaches to increase gastric residence time include mucoadhesion [3, 4], swelling and expanding systems and density controlled systems. The other approaches are super porous hydro gels, flotation modified shape systems [5], gastric emptying delaying devices and co administration of gastric emptying delaying drugs [6, 7].

In all the techniques floating drug delivery system (FDDS) is one of the simple, promising and practical approach to achieve increased gastric residence time. For immediate floating the density of the devices should be less than that of gastric contents. Based on the mechanism of buoyancy non effervescent and effervescent technologies are in FDDS [8]. Non effervescent systems use gel forming (or) highly swellable polymers and in effervescent systems matrices prepared with swellable polymers and inclusion of gas generating agents such as sodium bicarbonate, citric acid [9]. Floating property based on the evolution of CO_2 when in contact with acidic environment followed by the ability of the polymer gel to entrap it which decreases their density below one.

Pioglitazone hydrochloride is an oral anti diabetic agent used for the treatment of type-II diabetes comes under the class of thiazolidinedione Pioglitazone hydrochloride primarily act by enhancing peripheral glucose utilization. It has a short biological half life (3-7 h) and maintenance of steady state with once daily conventional form is very difficult. Thus the pharmacokinetic profile, maintenance of steady state concentration and better solubility in acidic medium has necessitated the development of sustained release gastro retentive dosage form of pioglitazone hydrochloride. In the present study, the

details of formulation development and evaluation of effervescent floating tablets of Pioglitazone hydrochloride are described.

Material and Methods

Pioglitazone hydrochloride was a generous gift from Dr. Reddy's laboratories, India. Hydroxypropyl methyl celluloses (HPMC K4M, K15M and K100M) were gift samples from Danmed Pharmaceuticals, India. Metalose 90SH, poly ethylene oxide (PEO) WSR 301 and PEO WSR coagulant were generous gift samples from Dow chemical company. Sodium bicarbonate (SBC), talc, magnesium stearate, lactose and micro crystalline cellulose (MCC) were purchased from S. D. Fine-Chem. Ltd., India. All other chemicals and reagents used were of analytical grade.

Experimental methods:

Preparation of floating matrix tablets with HPMC grades

Floating matrix tablets were prepared by wet granulation method. The compositions of all batches of matrix tablets were shown in Table 1. Accurately weighed quantities of Pioglitazone hydrochloride, SBC, various concentrations of retardant material (HPMC grades i.e. K4M/K15M/K100M/ Metalose 90 SH) and diluent (MCC) were taken in a mortar and screened through a # 44 mesh sieve (size: 350 µm) and mixed manually for 5 min for uniform composition. Then the premix blend was granulated with 2% PVP K30 in isopropyl alcohol. The wet mass was passed through # 22 mesh sieve (size: 700 µm). The granules were dried at 45 ± 5 ºC for 1 h and dried granules were sieved through # 25 mesh (size 600 µm). The dried granules were blended with lubricant mixture (1% magnesium stearate and 2% talc). The granules were compressed on a 16-station rotary tablet punching machine (M/S Cadmach, India) using 8-mm circular standard flat faced punches.

Preparation of floating matrix tablets with PEO grades

Composition of floating matrix tablets of Pioglitazone hydrochloride with different PEO grades (WSR 301 and WSR coagulant) were shown in Table 1. Tablets were formulated by the same wet granulation method described above, except the granulating agent was isopropyl alcohol instead of 2% PVP K30 in isopropyl alcohol.

Prior to compression granules were evaluated for their characteristic parameters such as angle of repose, loose bulk density (LBD), tapped density (TBD) and compressibility index (10).

Physical Characterizations of Compressed Tablets

The matrix tablets were evaluated for thickness (10 tablets) with digital screw gauge micrometer (Digimatic micrometer Series 293, Mitutoyo Corp, Japan), hardness (Monsanto tester, 6 tablets), mass variation (Digital balance Shimadzu, Japan, 20 tablets) and friability (Roche friabilator, Germany, 10 tablets).

Drug content in each batch of formulated tablets determined by randomly selecting 10 tablets and powdered. A quantity of powder equivalent to mass of one tablet was transferred into 100 mL volumetric flak containing 50 mL of pH 1.2 HCl followed by sonication for 1 h. The solution was made up to the mark with HCl (pH 1.2).The drug content was estimated by after suitable dilutions and measuring the absorbance at 266 nm using UV-visible spectrophotometer (Elico 161, India)

***In-vitro* buoyancy studies**

The buoyancy studies of all tablets were studied at 37 ± 0.5°C, in a 100 mL of pH 1.2 HCl. Floating lag time and total floating time (total duration of time the tablet remain buoyant) was observed. For the optimized batch digital photographs were taken after 1 min, 1, 3 and 6 h.

***In-vitro* dissolution studies**

In-vitro dissolution studies of prepared floating matrix tablets (3 tablets) were studied using USP 28 type II (paddle method) dissolution apparatus (Electro lab, India). The dissolution medium was 900 mL of HCl (1.2 pH) maintained a 37 ± 0.5°C and 50 rpm. Aliquots of 5 mL were collected at predetermined time intervals and replaced with equivalent volume of fresh hydrochloric acid buffer. Drug content in the samples were analyzed by spectrophotometrically at 269 nm.

Water uptake studies

Determination of water uptake the pre weighed tablets were introduced in to a USP 28 (United States Pharmacopoeia 24) dissolution apparatus-II containing 900 mL of pH 1.2 HCl maintaining 37 ± 0.5°C and rotation speed of 50 rpm. At selected time intervals the tablet was withdrawn and excess of fluid was blotted with tissue paper and weighed. Swelling of the tablet was expressed as % water uptake (%WU) calculated by the formula,

$$\%WU = \frac{(Wt - Wo)}{Wt} \times 100 \qquad \text{(Eq 1)}$$

Where Wt = the weight of the swollen tablet, Wo = the initial weight of the tablet.

***In-vivo* radiographic studies**

The protocol of radiographic studies on 3 healthy male human volunteers (weighing 55-75 kg and age group of 24 ± 2) was approved by the Institutional Human Ethical committee of K.L.R. Pharmacy College, Paloncha, India, affiliated to Kakatiya University. A written consent was taken from the volunteers before participation, a physician and a radiologist were supervised these studies. Optimized formulation was modified by adding 25 mg X-ray grade barium sulphate (10 mg of drug and 15 mg of MCC were replaced).The tablet was given to the every volunteer with a glass of water, after overnight fasting. X-ray images were taken after 1, 2, 4, and 6 h .The mean gastric residence time was calculated.

Kinetic analysis of dissolution data

To analyze the release kinetics *in-vitro* dissolution data was fitted into zero-order, first- order [11] and Higuchi [12]. For determination of mechanism of drug release the data was fitted into Korsmeyer-Peppas equation [13, 14]. By using the theoretical release profile [15] *in-vitro* dissolution profiles were compared with similarity factor (*f2*). The two dissolution profiles were considered to be similar if *f*2 values were in between 50-100. From the

dissolution profiles of each formulation, the dissolution efficiency (DE) [16] was determined at 2, 6, and 8 h.

Fourier transform infrared spectroscopy (FTIR) & Differential scanning calorimetric (DSC) studies

Compatibilities between used excipients and drug were tested by performing FTIR and DSC studies. Infrared spectrum of pure drug and physical mixture of drug and excipients (1:1 ratio) were recorded between 400 to 4000 cm^{-1} on FTIR instrument (FTIR 8400 S Shimadzu). The IR spectra for the test samples were obtained using potassium bromide disc method.

DSC studies done for pure drug and optimized formulation using DSC-6, Perkin Elmer USA. In a flat bottom aluminum cells the samples were hermetically sealed and heated between 50-400°C under a nitrogen purge of 40 mL min^{-1}.

Results and Discussion

Physical evaluation of granules and matrix tablets

The results of angle of repose and compressibility index (%) ranged from 18.3-22.2º and 11.1-13.8 % respectively. The results of angle of repose (<30) indicate good flow properties of the granules. This was further supported by lower compressibility index values. Generally compressibility index values less than 15 % results in good to excellent flow properties [17]. The results of LBD and TBD ranged from 0.21-0.22 gm/cc and 0.84-0.86 gm/cc respectively. All these results indicate that the granules possessed satisfactory flow properties and compressibility index.

Uniform conditions were maintained to prevent processing variables. Mean thickness of tablet was 3.3 ± 0.4 mm, mean hardness 3.5 ± 0.6 kg cm^{-2} , average mass variation 200 ± 3 mg and friability ranged from 0.5 to 0.8%. The content uniformity of the tablets was 98.6 ± 2.3 %. All the post compression parameters of floating matrix tablets were in house specifications.

***In- vitro* buoyancy studies**

Sodium bicarbonate (SBC) was used as effervescent base. For optimum *in-vitro* buoyancy and floating lag time initially formulations were prepared with different concentrations of SBC (7.5, 10, 12.5 and 15%). The interaction of acidic fluid with SBC results in formation of CO2 followed by swelling polymer gel entraps CO_2 which decreases its density and causes continued floatation. As the concentration of SBC increased the floating lag time was decreased (Whitehead et al. 1998). In the present study 15% of SBC (30 mg) selected because less lag time (25-40 sec) and rigidity throughout the study.

Tablets with HPMC K4M and PEO WSR 301, their low viscosity causes delayed gel formation and subsequent increase in floating lag time and decreased total floating duration (< 8 h) compared to the tablets prepared with higher viscosity grades of HPMC and PEO. Except above 2 grades of polymers remaining batches of all tablets floats instantaneously within one minute only.

Water uptake studies

For sustained release formulations rate controlling mechanisms were diffusion, swelling and erosion. % swelling can be studied by water up take studies and shown in Figure 1.When the amount of polymer increased from 15 to 20 % in all grades of HPMC swelling of polymer increased , erosion decreased and matrix integrity was maintained for enough time. The same results obtained in PEO grades also. Compared to WSR 301, WSR coagulant showed highest swelling as the viscosity was more. In all grades of HPMC and PEOs Metalose 90SH was higher viscosity (2, 00,000) grade of HPMC polymer showed highest swelling and matrix integrity was more than 12 h.

***In- vitro* dissolution studies**

Theoretical drug release of Pioglitazone hydrochloride was calculated by using pharmacokinetic parameters [15]. Floating tablets were formulated to achieve steady state plasma concentration and drug release with predetermined kinetics. Initially floating tablets were prepared with low viscosity grade HPMC K4M in different concentrations (10, 15 and 20%) (not shown). *In-vitro* dissolution studies of K4M showed that all tablets were completely disintegrated with in 5 h and UV analysis showed that 100% drug released from the formulations. Further increase in HPMC K4M didn't significantly affect the release rate. Hence the viscosity of HPMC was increased in order to achieve the tablet integrity and the desired release profile. *In-vitro* dissolution profiles of formulations F1 to F3 containing 10, 15 and 20% of HPMC K15M respectively were shown in Figure 2a. From F1and F2 98.95, 99% of drug released after 8 and 10 h respectively. In both formulations faster drug release was due to less gel strength and low viscosity. F3 released 95.6% for 12 h. These results showed as the polymer concentration was increased drug retardation also increased. Drug release of from F4 to F6, composed of HPMC K100M was also shown in Figure 2b. The percentages of drug released from these formulations were 92.90, 85.3 and 72.08 respectively for 12 h. The drug release rate was inversely proportional to the polymer present in the matrix. As the concentration and viscosity increases the rate and extent of drug release was retarded due to controlling the matrix hydration with high molecular weight HPMC [18].

F7-F9 released (Metalose 90SH) 81.04%, 72.58% and 67.53% respectively for 12 h (Figure 2b). Higher viscosity Metalose 90SH (2, 00,000) had highest gel strength and more tortuosity. When this polymer exposed to dissolution medium, the rate of hydration was fast and maximum swelling followed by slow chain relaxation leads to a viscous gelatinous layer and drug release from this layer was very slow [19].

The results of dissolution studies of PEO WSR 301(F10-F12) and WSR coagulant (F13-F15) were shown in Figure 2c. Formulations F10, F11 failed to maintain their integrity and total drug release occurs with in 6, 10 h respectively. F12 released 90.1% for 12 h. F13 released 98.91% for 10 h. F14, F15 released 82.4, 73.2% of drug respectively for 12 h of testing intervals.

The drug release rate was decreased in the order of HPMC K4M > PEO WSR 303 > K15M > WSR Coagulant > K100M > Metalose 90SH, this was probably attributed to difference in swelling behavior of the polymers. With increasing molecular weight, the entanglement of polymer chain increased and mobility of macromolecules in the fully

swollen system decreases, this leads to retardation of drug release.

Kinetic analysis of dissolution data

Kinetic analysis of Pioglitazone hydrochloride floating matrix tablets were showed in Table 2. The results showed that all formulations were best fitted with Higuchi [12] and first order [11] as the R^2 values were highest. For determination of drug release the data was fitted into Korsmeyer-Peppas model [13, 14]. The value of 'n' is 0.58 – 0.82, indicating release was non-Fickian diffusion ($0.45 < n < 0.89$).

The optimized formulation was selected based on the similarity factor (*f2*) value, dissolution efficiency [16]. The similarity factor (*f2*) of F3 was compared with theoretical release profile was found to be 70.1, which was higher compared to all formulations. F3 showed that release was same as compared to theoretical release.

Fourier transform infrared spectroscopy (FTIR) & Differential scanning calorimetric (DSC) studies

The FTIR spectra of pure Pioglitazone hydrochloride showed peaks at 2928.1cm^{-2}(NH stretching), 1743.3 cm^{-2} (C=O stretching), 1617.86 cm^{-2} (C=O stretching, acid), 1615.9 cm^{-2} (aromatic ring), 1243.2 cm^{-2} (C-O-Aryl group). The optimized formulation gave same peaks. So there was no drug excipient interaction .This was further supported by DSC studies.

Figure 3 represents the DSC curves of pure drug and optimized formulation (F3). DSC thermogram of pure Pioglitazone hydrochloride showed sharp endothermic peak at 195.18°C and the optimized formulation peak was observed at 192.01°C. This revealed that there was no interaction between drug and the excipients used in the formulation.

***In- vivo* X-ray studies**

Radiograms monitored the duration of the tablet presence in stomach and small intestine after 3 h ingestion of the tablet. The tablet was not adhered to the gastric mucosa; the mean gastric residence time was 7.1± 0.2 hrs (Figure 4).

Conclusion

The effervescent FDDS is a promising approach to achieve *in vitro* buoyancy by using gel forming polymers HPMC K15M, HPMC K 100M, Metalose 90SH, PEO 301 and PEO WSR Coagulant in low concentration by employing sodium bicarbonate as gas generating agent. Among the various FDDS formulations studied, the formulation prepared with HPMC K15 M in the concentration of 20% showed the best result in terms of the required lag time (instantaneous floating), 12 h floating duration and 97.39 % drug release in 12 h is considered as the ideal formulation. The dosage form can control the release, avoid dose dumping and extend the duration of action of a drug with prolonged floating time.

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Table 1: Composition of pioglitazone hydrochloride (30 mg) effervescent floating matrix tablets

Form-ulation	HPMC K15M (mg)	HPMC K100M (mg)	Metalose 90SH (mg)	PEO WSR 301	PEO WSR coagulant (mg)	MCC (mg)	PVP K30 (mg)	Isopropyl alcohol (ml)	Total Weight
F1	20	-	-	-	-	110	4	Q.S.	200
F2	30	-	-	-	-	100	4	Q.S.	200
F3	40	-	-	-	-	90	4	Q.S.	200
F4	-	20	-	-	-	110	4	Q.S.	200
F5	-	30	-	-	-	100	4	Q.S.	200
F6	-	40	-	-	-	90	4	Q.S.	200
F7	-	-	20	-	-	110	4	Q.S.	200
F8	-	-	30	-	-	100	4	Q.S.	200
F9	-	-	40	-	-	90	4	Q.S.	200
F10	-	-	-	20	-	114	-	Q.S.	200
F11	--	-	-	30	-	104	-	Q.S.	200
F12	-	-	-	40	-	94	-	Q.S.	200
F13	-	-	-	-	20	114	-	Q.S.	200
F14	-	-	-	-	30	104	-	Q.S.	200
F15	-	-	-	-	40	94	-	Q.S.	200

Table 2: *In-vitro* release kinetics of pioglitazone hydrochloride effervescent

Formulation	R^2			n
	First-order	Zero-order	Higuchi	
F1	0.955	0.805	0.942	0.58
F2	0.871	0.955	0.963	0.59
F3	0.976	0.882	0.971	0.62
F4	0.882	0.963	0.973	0.51
F5	0.943	0.839	0.978	0.52
F6	0.978	0.954	0.988	0.61
F7	0.988	0.911	0.994	0.82
F8	0.969	0.972	0.959	0.64
F9	0.962	0.982	0.929	0.67
F10	0.909	0.768	0.954	0.58
F11	0.816	0.903	0.989	0.61
F12	0.966	0.964	0.981	0.82
F13	0.852	0.758	0.944	0.58
F14	0.948	0.983	0.885	0.82
F15	0.928	0.912	0.956	0.74

Table 3: Dissolution parameters, and *f2* factor of pioglitazone hydrochloride floating tablets

Formulation	Dissolution efficiency (%)[a]			
	2 h	6h	8h	*f2* factor
Theoretical	38.3	63.5	75.43	-
F1	56.8	99.4	b	51.2
F2	39.7	57.9	66.8	52.1
F3	36.1	50.4	63.7	70.1
F4	46.2	63.9	75.4	67.2
F5	28.3	51.4	59.9	65.1
F6	22.1	42.2	52.3	52.1
F7	34.8	46.3	68.1	54.5
F8	24.1	42.2	51.8	55.6
F9	16.9	31.2	38.4	58.2
F10	68.1	85.1	c	50
F11	44.5	77.8	88.2	51.3
F12	35.5	61.2	74.2	62.4
F13	43.5	66.5	78.1	69.1
F14	30.9	61.5	72.1	63.5
F15	21.8	49.3	56.2	62.5

[a] Mean ± SD, n=3.
[b] 97.7 % drug released in 6 h.
[c] 98.1 % drug released in7 h.

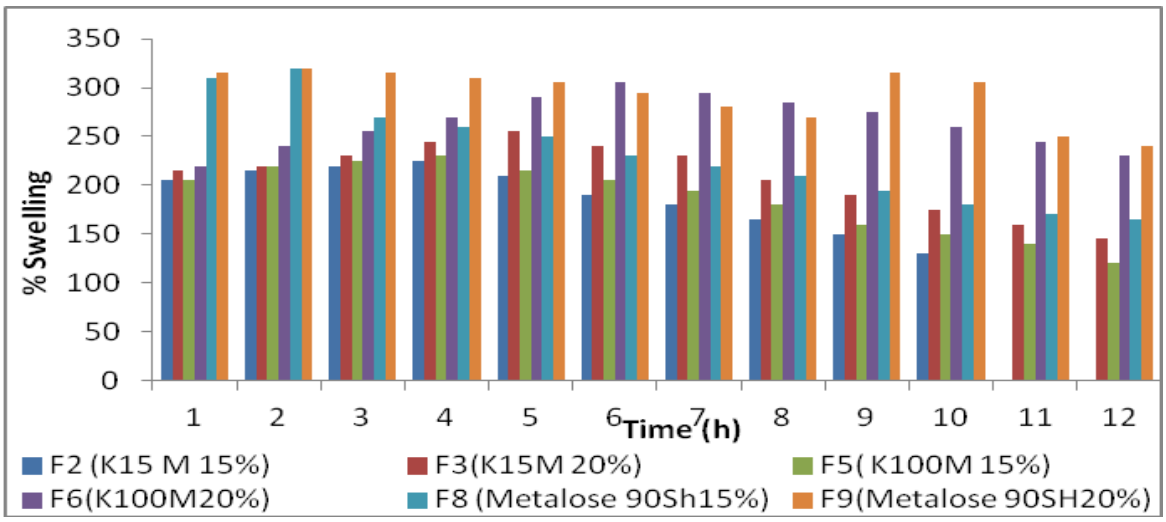

Figure 1: Percent swelling indexes of HPMC K15M, K100M and Metalose 90SH polymers at 15 and 20% concentrations

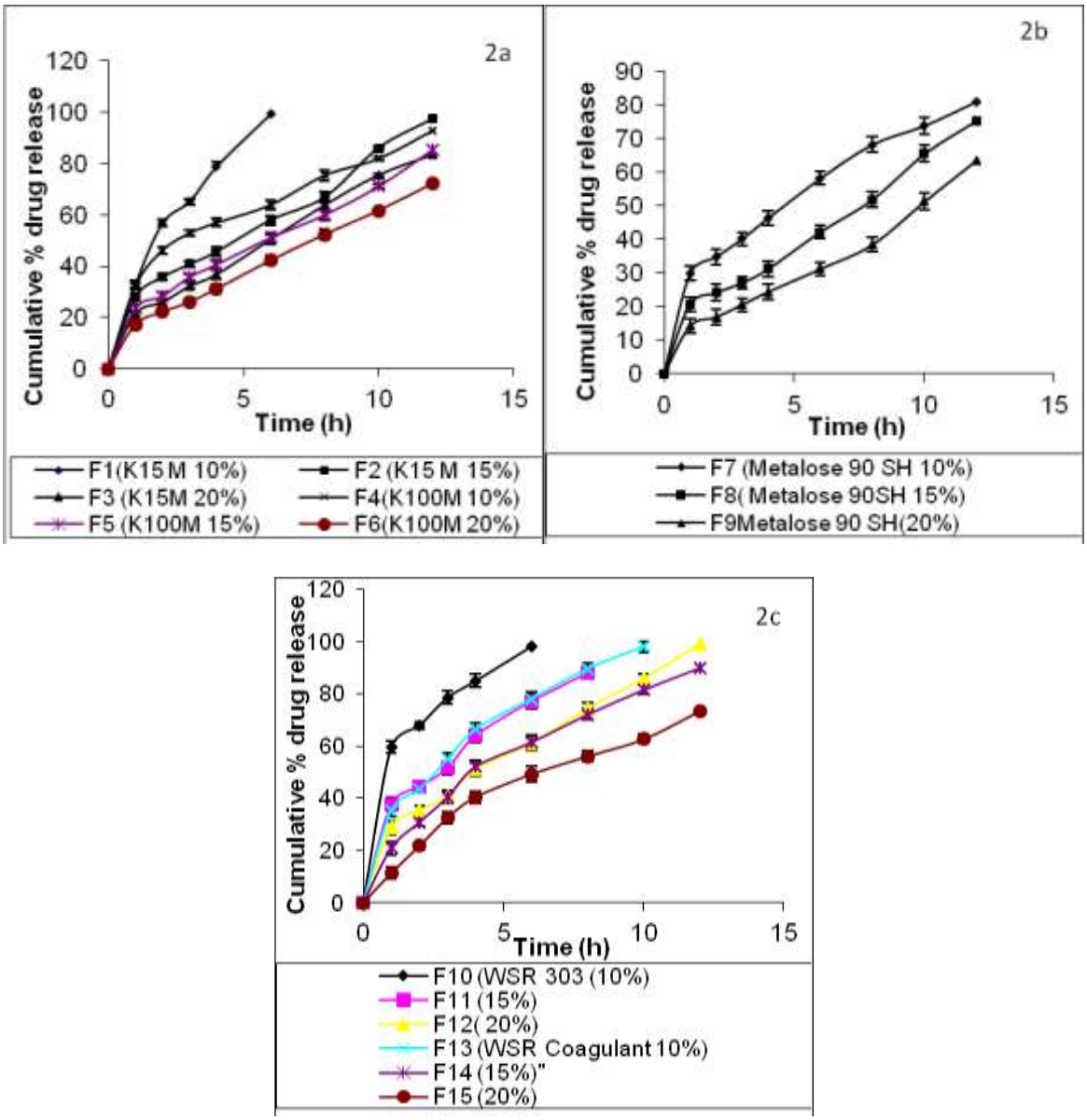

Figure 2: Cumulative % drug release profiles of Pioglitazone hydrochloride floating matrix tablets prepared with 10, 15 and 20% polymer concentrations of a) HPMC K15 & K100M, b) Metalose 90 SH, c) PEO WSR 301 & WSR Coagulant

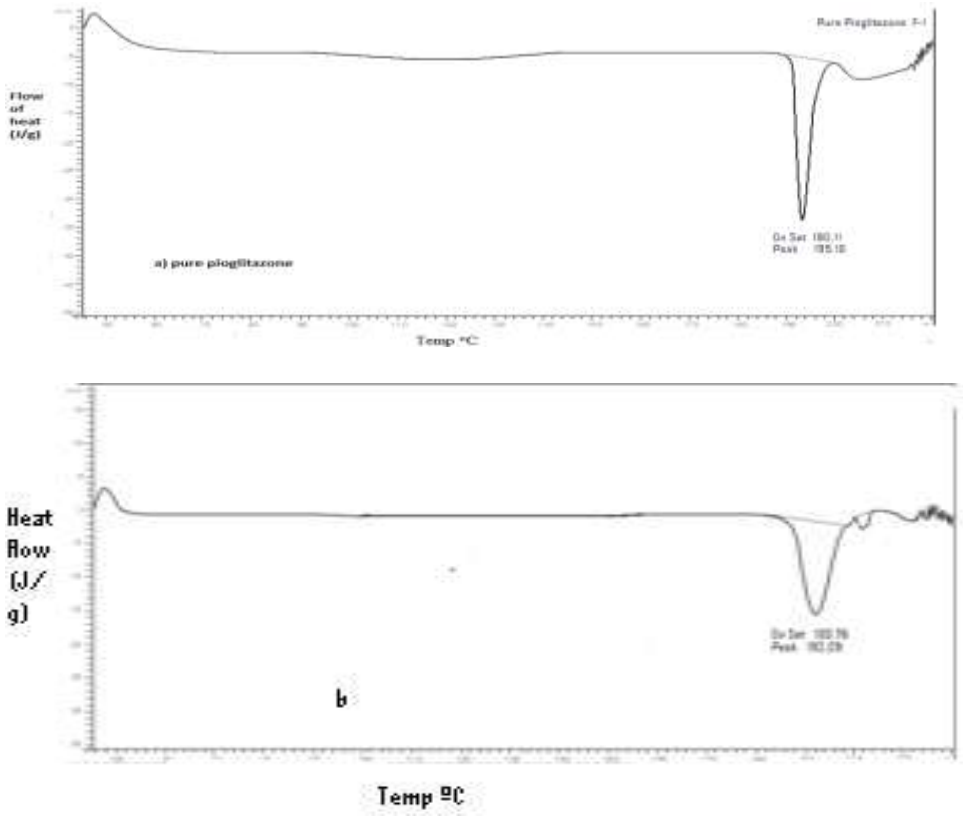

Figure 3: DSC curves of a) Pure Pioglitazone hydrochloride, (b) Optimized formulation F3

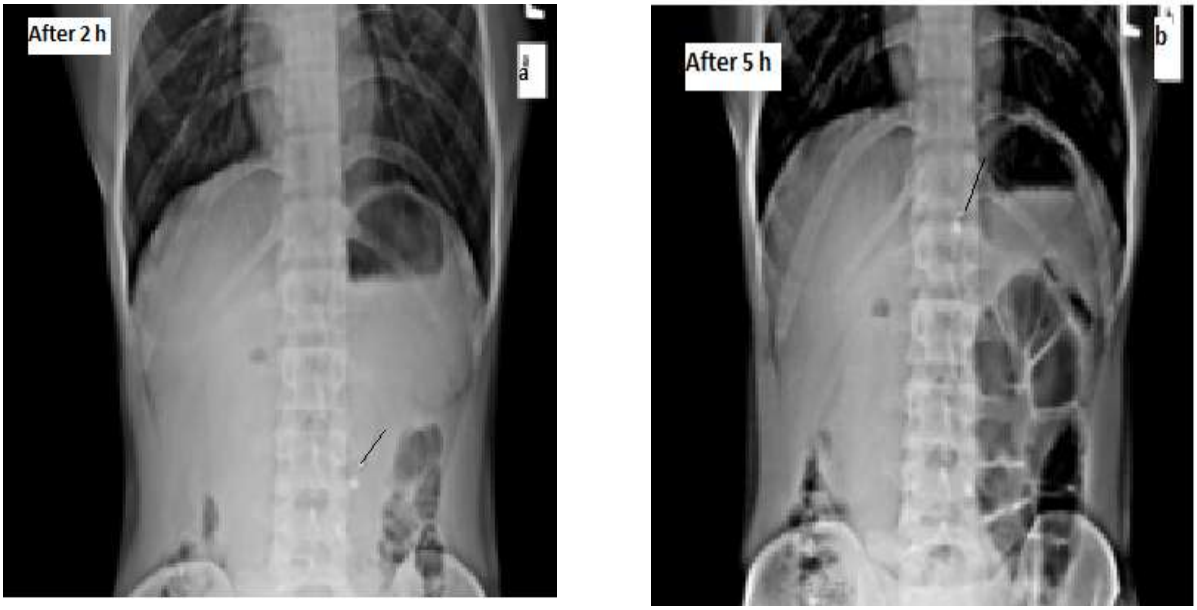

Figure 4: X-ray radiographic images of abdomen after 2 and 5 h of ingestion of $BaSO_4$ loaded optimized F3 effervescent floating tablet

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