ISSN 0976 – 3333

Available Online at www.ijpba.info

International Journal of Pharmaceutical & Biological Archives 2012; 3(1):204-210

ORIGINAL RESEARCH ARTICLE

Design and *In-vitro* Evaluation of Gastro Retentive Bilayer Floating Tablets of Rosiglitazone Maleate

Shrishail S Patil*[1], Doddyya Hiremath[1], K. Mahaboob Basha[1], R. H. Udupi[2]

[1]Department of Pharmaceutics, [2]Department of Pharmaceutical Chemistry, NET Pharmacy College, Navodaya Nagar, Mantralayam Road, Raichur – 584103, Karnataka

Received 02 Nov 2011; Revised 24 Jan 2012; Accepted 30 Jan 2012

ABSRTACT

In the present study, rosiglitazone maleate, a novel anti-diabetic agent, was formulated into Gastroretentive bilayer floating tablets and evaluated for various physico chemical properties. The immediate release layer was formulated using different super disintegrants and controlled release layer using Hydroxypropyl methylcellulose K100M (HPMC K100M) by direct compression method. Among various super disintegrants used, cross caramellose at the concentration of 8% was found sufficient to cause rapid drug release whereas 50% HPMC of the total weight of the tablet effectively controlled the drug release over a period of 24 h. Sodium bicarbonate at the concentration of 14 %w/w reduced the buoyancy lag time to less than 3 minute for the optimized tablet (F5). The total floating time for different formulations was in the range of 10-28 h. The concentration of HPMC has marked influence on the drug release from the prepared floating tablets. Release profiles indicated that, increasing the polymer concentration has drastically retarded the release of Rosiglitazone maleate. The optimized tablets F5 showed controlled and complete drug release over a period of 24 h. Tablets followed diffusion controlled first order kinetics. FT-IR and DSC studies revealed the absence of any chemical interaction between drug and polymer used. During the stability period optimized formulation was found to be stable with respect to physico-chemical and drug release characteristics.

Key words: Rosiglitazone maleate, HPMC K100M, Floating tablets; Direct compression; Buoyancy; Swelling; *In vitro* release.

INTRODUCTION

"Genetics loads the Gun, Life style pulls the trigger". There are many diseases that are caused due to genetic disorders, and are one of the causes for Diabetes Mellitus [1]. Diabetes Mellitus (DM) is a group of syndromes and chronic metabolic disorder characterized by hyperglycemia, altered metabolism of lipids, carbohydrates and proteins because of a lack of, or ineffective use of the hormone insulin and associated with reduced life expectancy, significant morbidity due to specific diabetes related micro vascular complications and diminished quality of life[2]. A fasting blood glucose level of 126 mg /dl and 200mg/dl post prandial (oral Glucose load) is considered as indication of DM [3].

The gastroretention of dosage form has been successfully utilized for drug delivery of narrow absorption window drugs [4,5]. In addition to retention in stomach region, the drug release can also be controlled for longer duration.[6] Several approaches have been utilized for gastroretention of dosage form like, floating tablets, in-situ gelling gums[7], multiunit systems[8] etc. Both matrix [9] and bilayer tablets [10] have been successfully developed and evaluated by several authors earlier. Bilayer tablets contain separate drug release layer and floating layer. Floating layer generally contains mixture of hydrophilic polymer and sodium bicarbonate. Sodium bicarbonate particles provide buoyancy by carbon dioxide bubble formation whereas gel matrix of hydrophilic polymer tries to entrap carbon dioxide bubbles.

Rosiglitazone maleate, chemically (±)-5-[[4- [2-(methyl-2-pyridinylamino) ethoxy] -phenyl] methyl] -2, 4-thiazolidinedione, (Z)-2-butenedioate, is a potent new oral antihyperglicemic agent that reduces insulin resistance in patients with type 2 diabetics by

***Corresponding Author:** Shrishail S Patil**, Email:** shailpharma@gmail.com

binding to peroxisomes to proliferate activated receptors (PPAR) [11-13]. The half-life of rosiglitazone maleate is 3-4 h and it reaches a peak plasma concentration after 1 h. It is highly soluble in 0.1 mol/l HCl (11.803 mg/ml) and its solubility decreases with increasing pH over the physiological range [14,15,16], therefore suggesting the need to develop dosage forms that can retain the drug in the stomach for better absorption. In light of the above factors, the present study was undertaken to design and evaluate bilayer gastro retentive floating tablets with an aim to achieve rapid onset of action there after controlled release of the drug through immediate release layer and controlled release layer.

MATERIALS AND METHODS

Rosiglitazone maleate was purchased from Yarrow Chem. Pvt. Ltd., Mumbai. Hydroxypropylmethylcellulose K100M was gifted from Colorcon Ltd., Goa. Sodium starch glycolate and Cross Carmellose sodium was gifted from S.Zaveri Pharma Ken Ltd., Mumbia. Carbopol 934P and Sodium bicarbonate was purchased from S.D Fine Chemicals, Mumbai. All other ingredients used were of analytical grades.

Preparation of bilayer floating tablets:

Dose calculation [17]

For sustained drug release up to 24 h, the total dose of drug required was calculated based on the fact that the conventional dose was 2 mg. The total dose was calculated using the following equation,

$$Dt = Dose\ (1 + 0.693 \times t/t_{1/2})$$

Where, Dt = Total dose, Dose = Immediate release dose,

t = Total time period for which sustained release is required,

$t_{1/2}$ = Half-life of drug.

Therefore, the required dose of rosiglitazone maleate is:

$$Dt = 2\ [1+ (0.693 \times 24)/3.5)]$$

Dt = 11.50 mg rosiglitazone and 15.2348 mg rosiglitazone maleate is equivalent to 11.50 mg rosiglitazone.

Design of bilayer tablets:

The bilayer floating tablets of Rosiglitazone maleate were prepared by direct compression method using 4 mm flat-faced punch of 10 station Rimek compression machine.

Sustain release layer

For the preparation of sustain release layer, the active ingredient was thoroughly mixed with polymer, diluent (MCC) and gas forming agent (sodium bicarbonate) using a mortar and pestle for 10 min; magnesium stearate and talc were added to the above blend as flow promoters. In all the formulations, the amount of Rosiglitazone maleate was kept constant at 12.58 mg and HPMC K100M was used in different concentrations i.e., 25, 37.5 and 50% respectively (Table 2).

Immediate release layer:

IR layer containing drug (2.65mg), super disintegrating agent, diluent and lubricants were mixed uniformly and compressed over SR layered tablet to obtain bilayer floating tablets. The formulation details are given in (Table 1).

Compatibility Studies:

Fourier Transform Infrared Spectroscopy:

The Fourier transform infrared (FT-IR) spectra of samples were obtained using FT-IR spectrophotometer (Shimadzu, 8400 S, Japan). About 2–3 mg of samples was mixed with dried potassium bromide of equal weight and compressed to form a KBr disc. The samples were scanned from 400 to 4,000 cm^{-1}wave number.

Differential Scanning Calorimetry:

Differential scanning calorimetry (DSC) experiments were also carried out to characterize the physical state of Rosiglitazone maleate in bilayer floating tablets as well as to find out the presence of any interaction among drug and the excipients. The tablets were crushed and required quantity of powder was put in aluminum pan and hermetically sealed. The heating rate was 10°C/min; nitrogen served as purging gas and the system was cooled down by liquid nitrogen. The differential thermal analyzer (METTLAR STAR SW 9.20) was used for this purpose.

Swelling studies [18]:

The extent of swelling was measured in terms of % of weight gained by the tablet. One tablet from each formulation was weighed and kept in Petri dish containing 50 ml of 0.1N HCl solution. At the end of specified time intervals tablets were withdrawn from Petri dish and excess buffer blotted with tissue paper and weighed. The % of weight gained by the tablet was calculated by using following formula:

$$\text{Swelling index (\%)} = \frac{M_t - M_0}{M_0} \times 100$$

Where, M_t – weight of tablets at time‘t’; M_0 – weight of tablets at time ‘0’.

Buoyancy lag time determination and Total floating time [19]:

The *in vitro* buoyancy was determined by the floating lag time. The tablets were placed in a 100 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface for floating was

determined as the floating lag time and further floating duration of all tablets was determined by visual observation.

***In Vitro* Dissolution Studies [17]:**

The release rate of Rosiglitazone maleate from floating tablets was determined using United States Pharmacopeia (USP) Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 0.1M hydrochloric acid, at 37 ± 0.5°C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. Absorbance of these solutions was measured at 228 nm using a UV/Visible spectrophotometer. The percentage drug release was plotted against time to determine the release profile.

Drug Release Kinetics:

Drug release data was fitted with different release kinetics models. Zero order, First order, Higuchi model and Koresmeyer-Peppas model were utilized for evaluating the release kinetics.

Stability studies [20]:

Stability studies were carried out at 40^{o}C / 75% RH ± 5% for 30 days by storing the selected formulation in stability chamber (Lab-Care, Mumbai).

RESULTS AND DISCUSSION

Physico-chemical evaluation of tablets:

The tablets were found to be uniform with respect to thickness (4.89 to 5.11 mm) and hardness (6.0 to 6.4 kg/cm^2). The friability (0.20 to 0.51 %), weight variation (1.18 to 2.54%) and drug content (98.68 to 99.82 %) of different batch of tablets were found within prescribed limits. The result of the physico chemical evaluation of various floating tablets is given (Table 3).

Compatibility Studies

FT-IR analysis

Rosiglitazone maleate pure drug and the optimized tablet was subjected for FT-IR spectroscopic analysis for compatibility studies and to ascertain whether there is any interaction between the drug and excipients used. The IR spectra of rosiglitazone maleate and bilayer floating tablet were found to be identical. The characteristic IR absorption peaks of rosiglitazone maleate at C=N (1618 cm^{-1}), Ar-C-H (3099 cm^{-1}), aliphatic C-H (2949 cm^{-1}), C=O stretching at 1246 cm^{-1} NH (3440 cm^{-1}) C-O (1246 cm^{-1}), C-S (717 cm^{-1}) & C-N (1304 cm^{-1}) were present in bilayer floating tablet. The FT-IR spectra of the pure drug and formulation F5 indicated that characteristics peaks of rosiglitazone maleate were not altered including any change in their position, indicating no chemical interactions between the drug and carriers used. These results indicate absence of interaction between the drug and the other components of the formulation.

Differential Scanning Calorimetry (DSC)

DSC is very useful in the investigation of the thermal properties of tablets, providing both qualitative and quantitative information about the physicochemical state of drug inside the tablets. In the present investigation, DSC thermograms of pure drug, optimized formulation F5, are taken as shown in Fig. 7-8. The thermal properties of the drug and the mixture of the drug and polymers are of interest since this can help to ascertain the crystalline and amorphous status of the entrapped drug in the polymers to assess the interaction among different components of the formulation during the fabrication process.

The DSC thermogram of pure rosiglitazone maleate showed a sharp melting endothermic at temperature 125^{o}C. This melting endotherm was also observed for rosiglitazone maleate bilayer floating tablet (F5) at 124.09^{o}C indicating absence of drug and polymer interactions showed a relatively flat thermal profile indicative of the amorphous nature of the polymer.

Swelling study:

Swelling ratio describes the amount of water that is contained within the hydrogel at equilibrium and is a function of network structure, hydrophilicity and ionization of functional group. Swelling study was performed on all the batches of floating tablets for 24 h, while the plot of % swelling against time (h) is depicted in Fig.1. All the floating tablets were found intact throughout the period of swelling (10 to 24 h) in 0.1N HCl. The percentage of swelling index was proportionate to the polymer level. The swelling index increased with increasing polymer level in the tablets and for the optimized formulation it was found to be 225.67% at the end of 24 h study.

Buoyancy lag time and total floating time determination:

Optimization of gas generating agent concentration in the tablets was carried out by preparing tablets with different concentrations of sodium bicarbonate (10, 12, 14 and 16%) at a constant polymeric level of 50% (F3-F6) and evaluated for floating lag time.

Formulations prepared with 10% sodium bicarbonate showed floating lag time of more than 1 hr whereas with 12% sodium bicarbonate concentration, floating lag time was reduced to 30 to 45 min. It was further reduced to 2-3 min when the concentration of sodium bicarbonate was

increased to 14%. However, further increase in sodium bicarbonate concentration from 14 to 16% has not shown significant effect on floating lag time. Moreover, the increased amount of sodium bicarbonate caused a large amount of effervescence, which in turn resulted in pore formation, which led to rapid hydration of the polymer matrix resulting rapid drug release. The higher concentration of sodium bicarbonate also affected the matrix integrity of the floating tablets. Our observations were in accordance with Jadhav KR *et al*.

***In Vitro* Dissolution Studies:**

Immediate release layer:

Drug release ranged from 5-10min for different IR layer formulations and among the two superdisintegrants studied, crosscarmellose sodium at the concentration of 8% w/w showed almost 100% drug release within 5 min compared to sodium starch glycolate at the similar concentration. Presence of superdisintegrant in the immediate release layer showed faster disintegration of the layer. This can attributed to the extent of water uptake and consequently the strong swelling power of this disintegrant causing sufficient hydrodynamic pressure to induce complete disintegration. The release pattern from different IR formulations is shown in the (Fig 2).

Sustained release layer:

Effect of polymer level:

The release pattern of floating tablets composed of different polymeric concentrations like 25%, 37.5% and 50% are given in (Fig 3). The floating tablets (F1-F3) released about 96.86, 98.60 and 90.60 % of Rosiglitazone maleate at the end of 10^{th}, 16^{th} and 24 h respectively. As the polymer concentration in the prepared floating tablets was increased from 25% to 50% a proportionate decrease in the drug release was observed, which could be due to higher swelling and greater gel strength that caused the increase in path length for the drug to diffuse from the matrix. This observation can be correlated with the swelling studies which indicated that, as the concentration of polymer in the matrix tablets was increased, the swelling index was also increased.

Effect of sodium bicarbonate:

In another set of formulations (F4-F6), floating tablets were prepared by keeping the concentration of HPMC K100M at 50% and the level of sodium bicarbonate was varied at 12%, 14%, 16% and its effect on drug release was observed. Formulation F4, F5 and F6 showed drug release of 94.60, 97.47 and 98.27% at the end of 24 h and 20^{th} h respectively. A proportionate increase in drug release was observed with increasing concentrations of sodium bicarbonate in the tablets. However the formulation F6 containing 16% sodium bicarbonate concentration could not sustain the drug release over a period of 24 h and released all its contents at the end of 20^{th} h. This could be due large amount of effervescence, which in turn resulted in pore formation, which led to rapid hydration of the polymer matrix resulting rapid drug release. Hence the tablets composed of 50% HPMC and 14% sodium bicarbonate was selected as optimized formulation which resulted in complete and controlled drug release over a period of 24 h.

Mechanism of drug release:

The best with the highest correlation coefficient was shown for first order, Korsemayer-Peppas, Higuchi and zero order equations as given in (Table 4). The rate constants were calculated from the respective plots. When the data was plotted as per zero order kinetics, plots were obtained with lower correlation coefficient values ranging from 0.758-0.852. When the data was plotted as per first order kinetics, linear plots were obtained with high correlation coefficient values ranging from 0.957- 0.987 indicating the order of release was as per first order equation. When the drug release data was fitted to Higuchi equation, linear plots were obtained with high correlation coefficient values ranging from 0.951- 0.982 for all the formulations. The drug release was proportional to square root of time indicating that the drug release from the optimized floating tablets was diffusion controlled. The release data obtained were also put in Korsemayer-Peppas model in order to find out n values, which describe the drug release mechanism. The n values of different optimized floating tablet formulations were found in the range of 0.368 - 0.411 with high correlation coefficient values ranging from 0.974 - 0.988. Hence the above observations led us to conclude that, all the floating tablets followed fickian diffusion controlled first order kinetics.

Stability of the Product:

The stability study was conducted according to the relevant ICH guidelines. The optimized formulation (F5) was stored for a period of 1month at 40^{o}C / 75% RH ± 5%. The results indicated that, the tablets did not show any physical changes (hardness and friability) during the study period. The drug content was found above 96% and no significant variation was observed at the end of one month stability study.

In the present study, gastro retentive bilayer floating tablets were successively prepared and evaluated. The concentration of polymer and gas generating agent has marked influence on the drug release from the floating SR layer. IR layer released all its contents with 5 min which is desired for quicker onset of anti-diabetic action and there after drug release was controlled over a period of 24h from SR layer. Thus, the prepared tablets exhibited the satisfactory results for once daily administration of Rosiglitazone maleate.

Table1: Composition Of Rosiglitazone Maleate Immediate Release Layer

S.No	Ingredients (mg)	Formulation code							
		IR1	IR2	IR3	IR4	IR5	IR6	IR7	IR8
1	Drug	2.65	2.65	2.65	2.65	2.65	2.65	2.65	2.65
2	SSG	1.5	3.0	4.5	6.0	---	---	---	---
3	CCS	---	---	---	---	1.5	3.0	4.5	6.0
4	MCC	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
5	Mg.st	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
6	Talc	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
7	Total	75	75	75	75	75	75	75	75

Table 2: composition of rosiglitazone maleate bilayer floating tablets

Code	Drug	CCS	MCC	Drug	HPMCK 100M	$NaHCO_3$ (mg)	PVP K30	MCC	Mg.st	Talc	Total (mg)
F1	2.65	6	q.s	12.58	31.25	12.5	5	q.s	4	2	200
F2	2.65	6	q.s	12.58	46.87	12.5	5	q.s	4	2	200
F3	2.65	6	q.s	12.58	62.5	12.5	5	q.s	4	2	200
F4	2.65	6	q.s	12.58	62.5	15	5	q.s	4	2	200
F5	2.65	6	q.s	12.58	62.5	17.5	5	q.s	4	2	200
F6	2.65	6	q.s	12.58	62.5	20	5	q.s	4	2	200

Table 3: Physicochemical properties of rosiglitazone maleate floating bilayer tablets

Formulation code	Hardness (Kg/cm^2)	Thickness (mm)	Friability (%)	Drug content (%)	Buoyancy lag time (min)	Total floating time(hr)
F1	6.3±0.32	5.22±0.01	0.32±0.04	98.74±0.93	63	10
F2	6.4±0.52	5.19±0.03	0.31±0.02	97.00±1.02	68	16
F3	6.4±0.33	5.21±0.09	0.27±0.05	98.18±0.57	74	28
F4	6.2±0.23	5.19±0.02	0.31±0.01	96.07±0.42	41	24
F5	6.3±0.44	5.22±0.04	0.28±0.08	96.46±0.21	1.83	24
F6	6.4±0.49	5.18±0.05	0.35±0.06	98.28±0.66	1.65	20

Table 4: kinetic analysis of *in-vitro* release data for optimized bilayer floating tablet formulations of rosiglitazone maleate.

Code	Zero order		First order		Higuchi		Korsmeyer-peppas	
	n	r^2	n	r^2	n	r^2	n	r^2
F1	8.411	0.824	-0.144	0.987	31.04	0.982	0.393	0.987
F2	5.408	0.852	-0.105	0.957	25.00	0.986	0.411	0.983
F3	3.084	0.805	-0.039	0.979	18.11	0.968	0.378	0.988
F4	3.283	0.782	-0.059	0.986	19.47	0.959	0.368	0.987
F5	3.191	0.786	-0.048	0.987	18.90	0.961	0.371	0.987
F6	4.059	0.758	-0.079	0.982	22.03	0.951	0.384	0.974

Table 5: Physico-Chemical data of optimized bilayer floating tablets before and after stability studies at 40^oc / 75% rh ± 5%.

Code	Friability (%)		Drug content (%)		FLT (Sec)		TFT (hrs)	
	Before	After	Before	After	Before	After	Before	After
F5	0.28±0.08	0.33±0.03	96.46±0.21	96.22±0.32	110	116	24	24

Fig.1.Overlapping IR spectra of Pure drug and optimized bilayer floating tablets of Rosiglitazone maleate

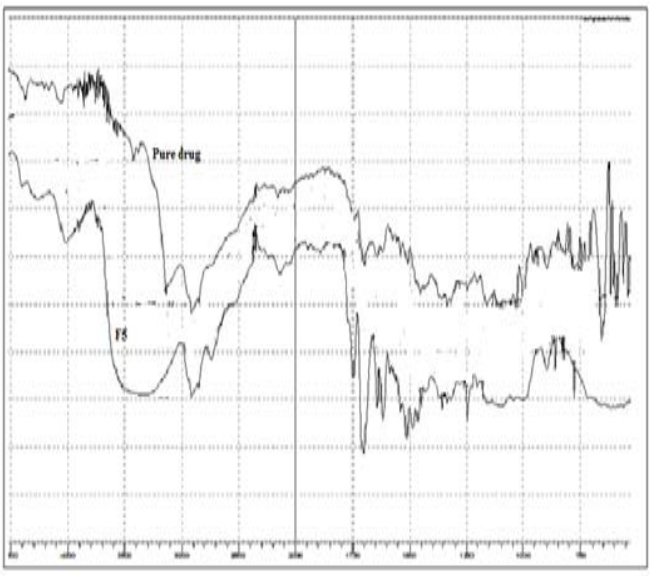


Fig 2: DSC thermogram of Pure drug and optimized formulation (F5)

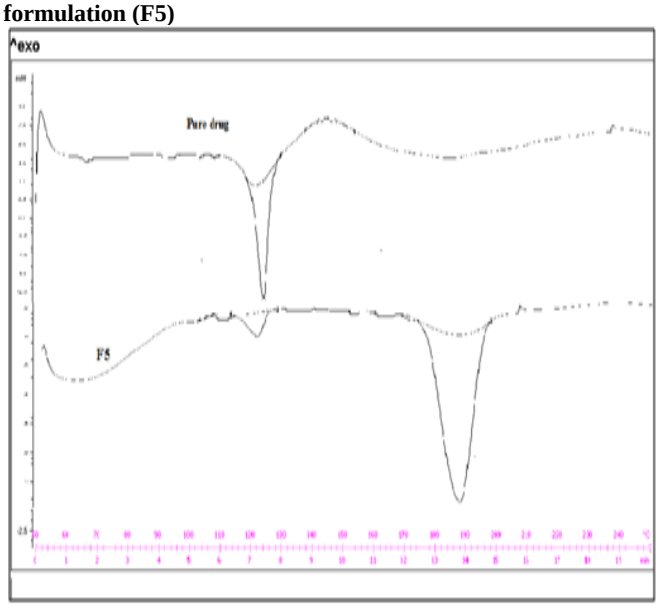


Fig 3: Photographs indicating the floating lag time of optimized formulation (F5)

Fig.4. Swelling study of different floating tablets of Rosiglitazone maleate

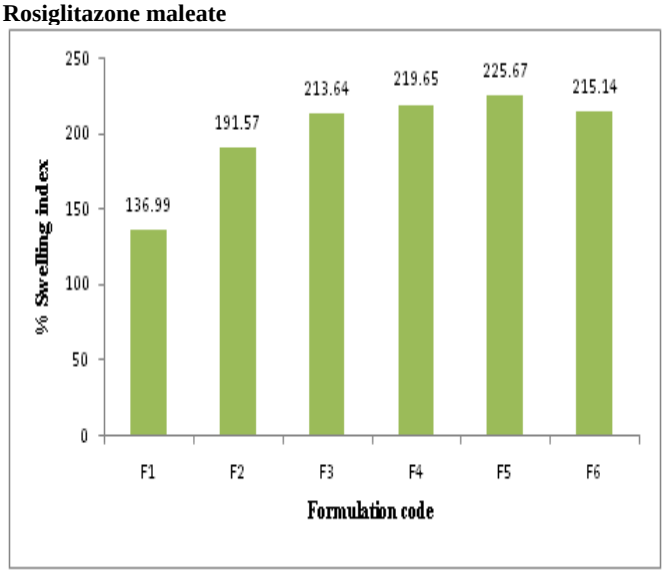


Fig.5. *In-vitro* release of Rosiglitazone maleate from immediate release layer in 0.1N HCl

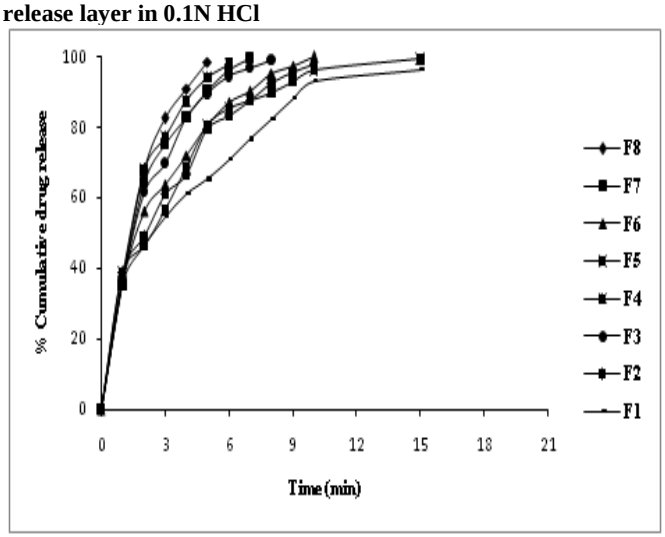
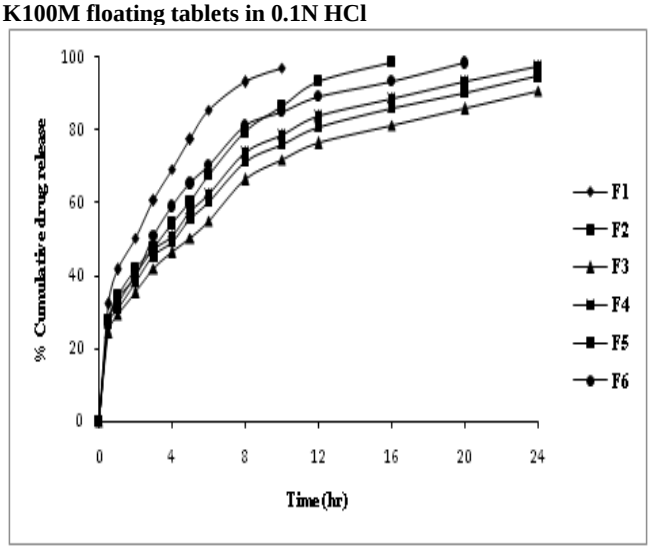


Fig 6: *In-vitro* release of Rosiglitazone maleate from HPMC K100M floating tablets in 0.1N HCl



ACKNOWLEDGEMENTS

The authors are thankful to the management of Navodaya Education Trust for providing

necessary facilities for carrying out the research work.

REFERENCES

1. Elas JL and Longo N. Glucose transporters. Annu Rev Med 1992; 43: 377-93.
2. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia, World Health Organization 2006: 1-46.
3. Drug evaluations annual, American Medical Association 1993; 109:35-38.
4. Talukder R and Fassihi R; "Gastroretentive Delivery Systems: A Mini Review". Drug Dev Ind Pharm. 2004; 30:1019-1028.
5. Arora S, Javed A, Ahuja A, Khar RK and Baboota S; "Floating drug delivery system: A review". AAPS Pharm Sci Tech. 2005; 6:E372-390.
6. Jacob S, Nair A B, Patil P N; "Design and evaluation of hydrophobic coated buoyant core as floating drug delivery system for sustained release of cisapride". Journal of Basic and Clinical Pharmacy. 2011; 2:11-19.
7. Rajinikanth P S, Balasubramaniam J and Mishra B; "Development and evaluation of a novel floating in situ gelling system of amoxicillin for eradication of Helicobacter pylori". Int. J. Pharm. 2007; 335: 114–122.
8. Jain S K and Gupta A; "Development of Gelucire 43/01 Beads of Metformin Hydrochloride for Floating Delivery". AAPS Pharm Sci Tech.2009; 4:1128-1136.
9. Abdelbary A, El-Gazayerly O N, NEl-Gendy N A, Ali A A; "Floating Tablet of Trimetazidine Dihydrochloride: An Approach for Extended Release with Zero-Order Kinetics". AAPS Pharm Sci Tech. 2010; 3:1058-1067.
10. Rahman Z, Ali M, Khar R K; "Design and evaluation of bilayer floating tablets of captopril". Acta Pharm. 2006; 56:49-57.
11. http://en.wikipedia.org/wiki/Diabetes
12. Kadhe G and Arasan RE. Advances in drug delivery of oral hypoglycemic Agents. Curr Sci 2002; 83(12): 1539-43.
13. Desvergne B, Wahli W: Peroxisome proliferator-activated receptors: nuclear control of metabolism. Endocr Rev 1999; 20:649-68.
14. Berger J, Moller DE: The mechanisms of action of PPARs. Annu Rev Med 2002; 53: 409-35.
15. Chawla A, Repa JJ, Evans RM, et al: Nuclear receptors and lipid physiology: opening the X-files. Science 2001; 294: 1866-70.
16. Chinetti G, Fruchart JC, Staels B: Peroxisome proliferator-activated receptors (PPARs): nuclear receptors at the cross-roads between lipid metabolism and inflammation. Inflamm Res 2000; 49: 497-505.
17. Sonar GS, Jain DK, More DM. Preparation and *in vitro* evaluation of bilayer and floating-bioadhesive tablets of Rosiglitazone maleate. Asian J Pharm Sci 2007; 2 (4):161-69.
18. Nerurkar J, Jun HW, Prince JC, Park MO. Controlled release matrix tablets of ibuprofen using cellulose ethers and carrageenans: effect of formulation factors on dissolution rate. Eur J Pharm Biopharm 2005; 61:56-68.
19. Puneeth KP, Kavitha K, Tamizh MT. Development and evaluation of rosiglitazone maleate floating tablets. Int J Appl Pharm 2010; 2(2):6-10.
20. Arjun G, Prasad MS, Santhosha D, Achaiah G. Formulation and evaluation of rosiglitazone mouth dissolving tablet. Int J Pharm Bio Sci 2010; 1(1):1-9.