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Journal of Chemical and Pharmaceutical Research

J. Chem. Pharm. Res., 2011, 3(4):140-149

ISSN No: 0975-7384
CODEN(USA): JCPRC5

Preparation and in vitro evaluation of rosiglitazone maleate bi layered bio adhesive floating tablets

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ABSTRACT

The present study includes preparation and optimization of Rosiglitazone maleate bi layered floating - bio adhesive tablets. The first layer is a fast releasing layer consisting of a loading dose of the drug prepared by wet granulation method while the second layer is a sustaining layer containing maintenance dose of the drug.The loading dose was directly compressed onto the sustaining layer. The scope of the present work focuses on the development of matrix floating tablet by incorporating a high dose of freely soluble active substance with high viscosity polymers achieving a sustained release for 24 hrs to target the stomach. Different grades of Hydroxypropylmethylcellulose K_4M, hydroxypropylmethylcellulose $K_{10}M$ and Sodiumcarboxymethylcellulose were used as swell able polymers. Drug-polymer compatibility was assessed by FTIR studies. The granules and tablets were subjected to evaluation of various pre compression and post compression parameters. Results were found to be within the acceptable limits. The results of in vitro release data indicate that for all formulations, drug release is through diffusion pathway and the mechanism of Rosiglitazone maleate release from the floating layer followed first order case II transport. Based on the results of t_{50}, optimized formulation was F5. Desired gastric retention and controlled drug delivery is achieved.

Key Words: Rosiglitazone maleate, Floating tablets, gastric retention.

INTRODUCTION

The oral route is a promising route of drug delivery. Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach. This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed. The gastric emptying of dosage forms in humans is affected by several factors because of which wide inter- and intra-

subject variations are observed .This may lead to non-uniform absorption and makes bio availability unpredictable.

One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time(GRT), with gastro retentive dosage form(GRDFs or GRDS). They prolong dosing interval and also increase patient compliance beyond the level of existing controlled release dosage forms which is a valuable asset. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion , floatation, sedimentation, expansion, modified shape system or by simultaneous administration of pharmacological agent that delay gastric emptying[1].

Floating drug delivery systems[2] have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the Gastric retention time. Addition of bio adhesive polymers will overcome the requirement for large quantity of fluid in the stomach for floatation. Rosiglitazone maleate is an oral anti diabetic agent, which acts primarily by increasing insulin sensitivity. A gastro retentive dosage form will release the drug over an extended period in the stomach and upper gastro intestinal tract thus enhancing the opportunity for absorption.

EXPERIMENTAL SECTION

Materials:

Rosiglitazone maleate (Lee pharma, Hyderabad), HPMC K_4M and $K_{10}M$, Sodium Carboxy Methyl Cellulose are from Aurobindo pharma, Hyderabad. Micro crystalline cellulose, talc, magnesium stearate, PVP K30, Soluble starch, Di- Calcium Phosphate, Tartarazine and Aerosol are supplied by Loba Chemie pvt. LTD

Methods:

Pre formulation (compatibility) studies [3][4]:

Compatibility of the drug with excipients was confirmed by FTIR studies. The pellets were prepared at high compaction pressure by using potassium bromide and the ratio of Rosiglitazone maleate to potassium bromide is 1:100. These were examined using Perkin Elmer spectrum RX1 FT-IR spectrometer model. The spectra of drug and other ingredients in the formulation were compared with that of the original spectra.

Formulation of bi layered sustained release floating tablets of Rosiglitazone maleate [5][6]

Calculation of Loading and Maintenance Dose:

The formulation involves the calculation of loading dose(Di) desired release rate(Ks), maintenance dose(Dm) and total dose needed for Rosiglitazone maleate bi layered SR floating tablets for twice daily administration as follows:

- Oral dose: 4 mg twice a day
- Dosing Interval (τ): 24 hours
- Elimination Half-life ($t_{1/2}$): 3-4 h
- Time of peak concentration (t_p): 1 hour
- Elimination rate constant (Ke): $0.693/ t_{1/2}$

  $= 0.693/4$

  $= 0.17325\ hr^{-1}$
- Loading dose (Di): Css.Vd / F

  But, $Css = F.Xo/ Ke.Vd.\tau$

Thus, Di = F.Xo / Ke.Vd.τ * Vd / F
= Xo / Ke. τ
= 4 / 0.17325*24
= 0.962 mg

- Desired rate of drug release (Ks): D_i * Ke
= 4 * 0.17325
= 0.693 mg / hr
- Maintenance dose (Dm): Ks * τ
= 0.693 * 24
= 16.632 mg

- Corrected initial dose (Di^*): Di – (Ks * t_p)
= 0.962 – (0.693 * 1)
= 0.269 mg
- Total dose (Dt): Dm + Di^*
= 16.632 + 0.269
= 16.901 mg
≡17 mg

Preparation of Bi layered Tablets [7]

Drug loading granules (immediate dose):

Prepared by mixing Rosiglitazone maleate, starch, PVP and di calcium phosphate using water as a wetting agent. Dried at 60º C for 30 minutes in an oven and then mixed with talc, Tartarazine and magnesium stearate. The composition was listed in table 1.

Floating granules (sustained dose):

Rosiglitazone maleate is mixed with different excipients as shown in table 2. The granules were then dried at the same conditions listed above.

Exactly 0.3 g of floating granules and 0.1 g of drug loading granules were weighed and compressed into bi layered tablets by a single punch tablet compression machine (Cadmach, Ahmadabad, India). A flat faced punch 12mm diameter was used. Each tablet contained 17mg (1mg as initial dose and 16mg as sustained dose of Rosiglitazone maleate).

Table 1: Composition of Drug Loading Layer of Bi layered Tablets

S.No	Composition	Quantity (mg)
1	Rosiglitazone maleate	1
2	Soluble starch	5
3	Poly vinyl pyrrolidone	4
4	Magnesium stearate	3
5	Talc	3
6	Tartarazine	2
7	Di calcium phosphate	82

Table 2: Composition of Floating Layer (mg)

COMPOSITION	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)	F6(mg)	F7(mg)	F8(mg)
Rosiglitazone maleate	16	16	16	16	16	16	16	16
HPMC K_4M	7.5	30	54	13.5	-	-	-	-
HPMC $K_{10}M$	-	-	-	-	54	7.5	13.5	30
SCMC	7.5	30	6	1.5	6	7.5	1.5	30
MCC	30	30	30	30	30	30	30	30
Aerosol	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Magnesium stearate	9	9	9	9	9	9	9	9
Di – calcium phosphate	229.25	184.25	184.25	229.25	184.25	229.25	229.25	184.25

Physical evaluation of tablets:

A) **Shape of Tablets:**

The compressed tablets were examined under the magnifying lens for the shape of the tablet.

B) **Tablet Dimensions:**

Thickness and diameter were measured using a Vernier Callipers

C) **Hardness [8]:**

The hardness of the tablets was determined using Monsanto hardness tester.

D) **Friability Test**:

The friability of tablets was determined using Roche friabilator. 20 tablets were initially weighed (w_0) and transferred into friabilator, operated at 25rpm for 4 minutes. The tablets were weighed again (w). The % friability was then calculated by

$$\text{Percentage of Friability} = 100\ (1\text{-}w/w_0)$$

E) **Weight Variation Test:**

Twenty tablets were selected at random and the average weight was determined. Not more than two of the individual weights deviate from the average weight by more than the percentage deviation shown in table and none deviates by more than twice the percentage.

F) **Tablet Density [9]:**

The tablet will float when its density is less than that of gastric fluid (1.004g/cc). When tablet contacts the test medium, tablet will be expanded (due to swell able polymers) and there was liberation of CO_2 gas (because of effervescent agent, sodium bicarbonate). The density decreased due to this expansion and upward force of CO_2 gas generation. This plays an important role in ensuring the floating capability of the dosage form.

G) **Buoyancy / Floating Test**:

The in-vitro buoyancy was determined by floating lag time. The tablets were placed in a 100 ml beaker containing 0.1N HCL. The time required for the table to rise to the surface and float was determined as floating lag time. The duration of time the dosage form constantly remained on the surface of the medium was determined as the total floating time.

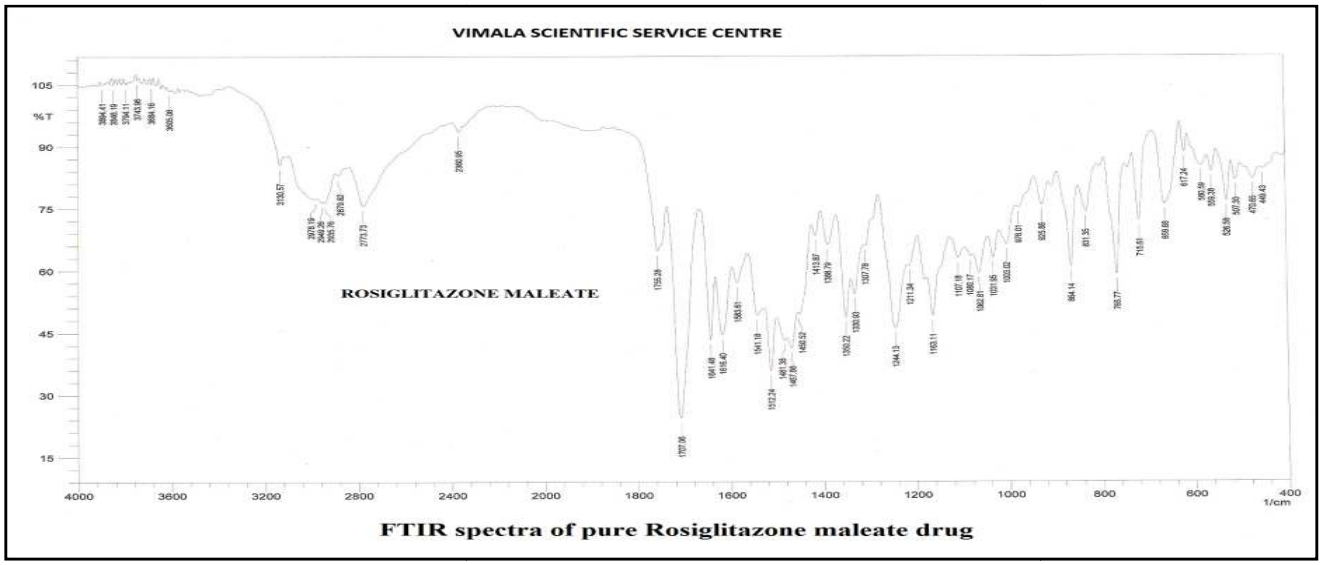
H) **Swelling Study [10]**:
The individual tablets were weighed accurately and kept in 50ml of water. Tablets were taken out carefully after 60min, blotted with filter paper to remove the water present on the surface and weighed accurately. Percentage swelling was calculated by using formula;

$$\text{Swelling study} = \text{wet weight} - \text{dry weight} / \text{dry weight} \times 100$$

I) **Test For Content Uniformity**
About 50 mg of Rosiglitazone maleate was weighed accurately, transferred into a 100 ml volumetric flask, dissolved, suitably diluted and made up to volume with 0.1 N HCl and mixed (standard preparation).Five tablets were powdered in a mortar. Then, powder equivalent to 50 mg of Rosiglitazone maleate was transferred to a 100 ml volumetric flask, 100 ml of 0.1 N HCl was added, sonicated for 30 min and filtered through 0.45µ membrane filter. It was then diluted to 1ml to 100ml (sample preparation). After making suitable dilutions, measured in a UV-visible Spectrophotometer at 318.5 nm using 0.1 N HCl as blank.

J) **In-Vitro Drug Release Study :**
In-vitro release studies were carried out using USP XXIII, paddle dissolution test apparatus. 900ml of simulated gastric fluid (pH 1.2) was taken in dissolution vessel and the medium was maintained at $37^0C \pm 0.5^0C$ temperature and 100 rpm speed. 1ml of sample was withdrawn at predetermined time intervals and same volume of fresh medium was replaced. The samples are analyzed for drug content against 0.1N HCl as a blank at λmax 240nm using U.V. Spectrophotometer.

Fig.1.1: FTIR spectra of Rosiglitazone maleate



FTIR spectra of pure Rosiglitazone maleate drug

RESULTS AND DISCUSSION

Pre formulation Studies: FTIR Study:
The characteristic functional groups of the pure Rosiglitazone maleate and physical mixtures of Rosiglitazone maleate and polymers showed the peaks at the following wave number region. Aromatic C=C stretching vibration 1641.48 cm^{-1} ; Carboxylic acid C=O stretching vibration 1211.34 cm^{-1}, 1107.18 cm^{-1}, 1031.95 cm^{-1}, 1003.02 cm^{-1}; Aromatic tertiary amine C-N stretching vibration 1244.13 cm^{-1}, 1163.11 cm^{-1}, 1062.81 cm^{-1}; Ketonic C=O stretching

vibration 1707.06 cm^{-1}, 1641.48 cm^{-1} .There was no appearance or disappearance of any characteristics peaks. This shows that there is no chemical interaction between the drug and the polymers used in the tablets. The FTIR spectra were in figures 1.1 to1.4.

Fig.1.2: FTIR Spectra of Rosiglitazone and HPMC K_4M

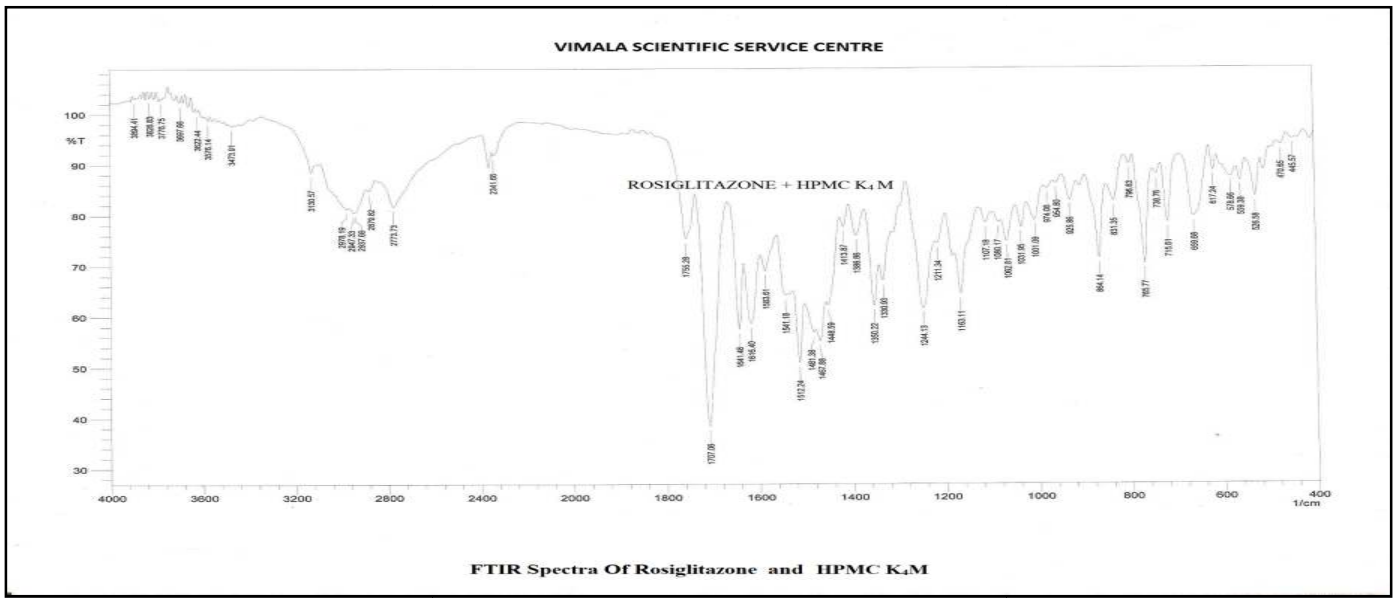
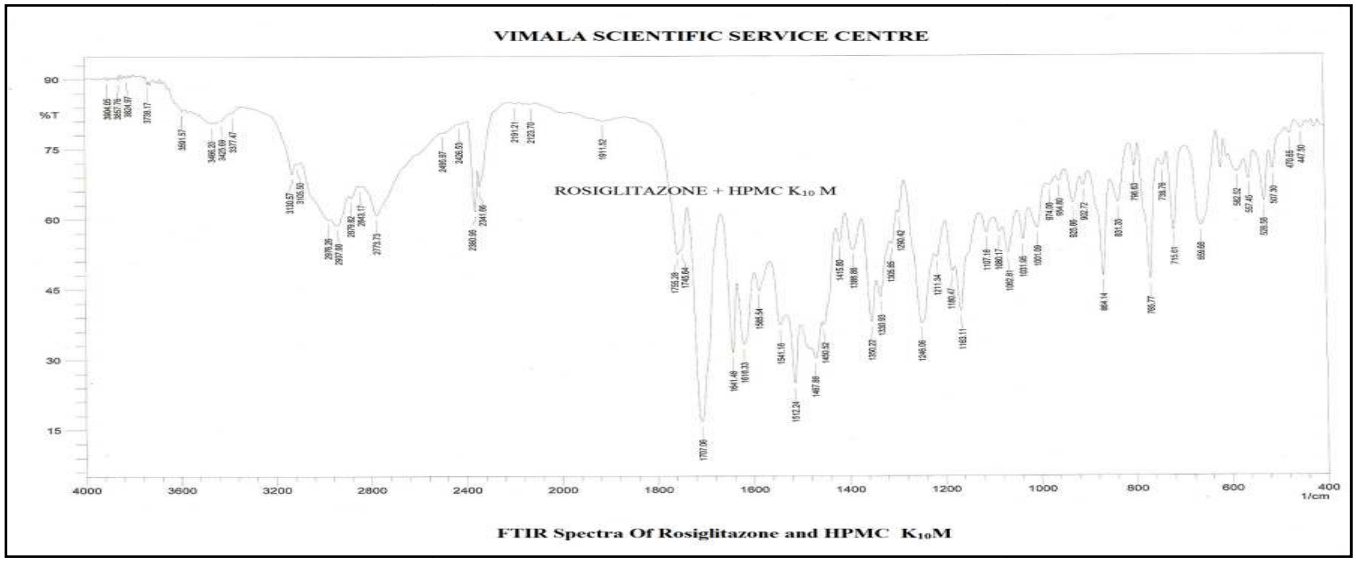


Fig.1.3: FTIR Spectra of Rosiglitazone and HPMCK $_{10}$M



The quality control tests adopted for the tablets were depicted in the tables 3.1 and 3.2. The hardness of the tablets is between 5.13±0.058 Kg/Cm^2 to 5.53±0.115 Kg/Cm^2 .The thickness of the tablets range between 5.78 ±0.151mm to 6.29±0.076mm and the diameter ranges from 11.453±0.188mm to 13.663±0.067mm .The percent friability of the prepared tablets is well within acceptable limit. The percentage friability of all batches range from 0.079±0.044% to 0.667±0.747% .There is no significant weight variation observed between average weight and individual weight. The drug content in all the formulations is within the range of 96.04±1.248% to 93.32±1.191%, ensuring uniformity. Density ranges from 0.433±0.007g/cc to 0.672±0.029 g/cc. The total floating time is between 25.4±0.418 hours to 30.5±0.354 hours and swelling index ranges from 76% to 84.04%.The swelling index for the formulations is shown in figure 2.

Fig1.4: FTIR Spectra of Rosiglitazone, SCMC, HPMCK$_4$M and HPMCK$_{10}$M

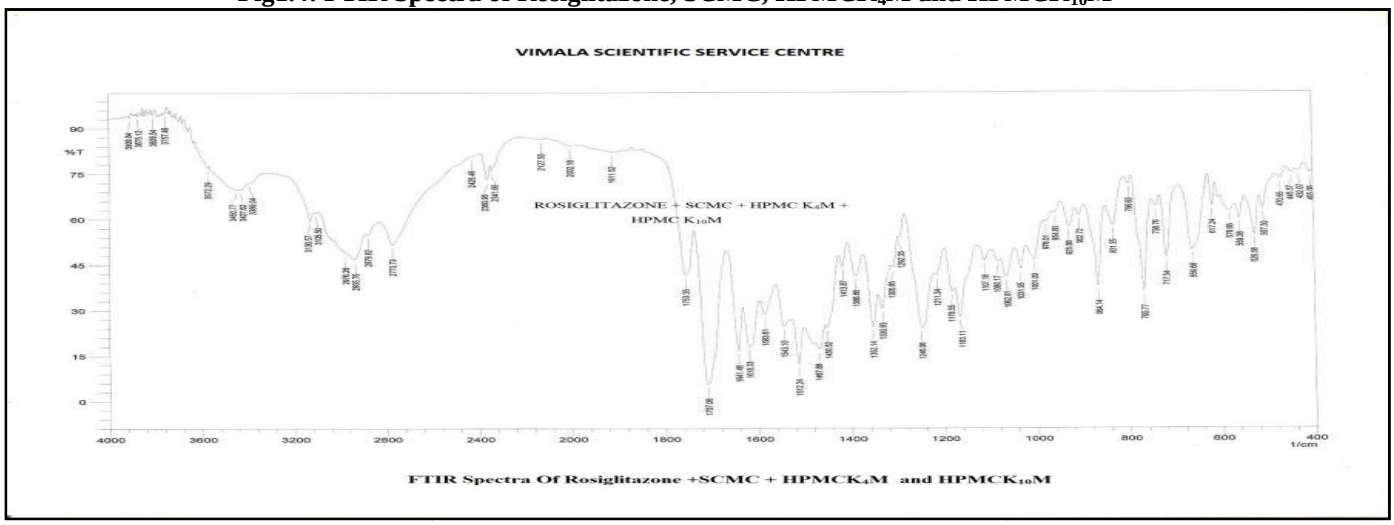


Table 3.1: Physical Evaluation of Tablets

Formulation code	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability%	Wt. Variation
F1	5.933±0.112	12.193±0.535	5.53±0.115	0.079±0.044	400.033±0.275
F2	5.78± 0.151	11.453±0.188	5.50±0.173	0.175±0.057	400.817±0.601
F3	6.2± 0.177	13.533±0.528	5.17±0.208	0.217±0.059	399.933±0.625
F4	6.157±0.13	12.927±0.405	5.20±0.265	0.212±0.059	400.067±0.601
F5	6.293±0.076	13.663±0.067	5.13±0.058	0.667±0.747	400.017±0.629
F6	6.12±0.139	12.9 ±0.164	5.37±0.208	0.258±0.036	400.617±0.473
F7	6.083±0.09	12.867±0.295	5.40±0.173	0.208±0.059	400.217±0.729
F8	6.04±0.092	12.63±0.104	5.47±0.306	0.225±0.108	400.45±0.737

All values expressed as mean± S.D, n=3

Table 3.2: Physical evaluation of Tablets

Formulation code	Drug content Uniformity%	Tablet Density (gm/cc)	Floating Time (hrs)
F1	96.04±1.248	0.58±0.039	25.8±0.57
F2	96.39±0.617	0.672±0.029	27.7±0.57
F3	97.88±1.184	0.45±0.026	29.6±0.652
F4	97.44±0.976	0.497±0.04	26.4±0.418
F5	98.32±1.191	0.433±0.007	30.5±0.354
F6	97.36±0.883	0.503±0.022	25.4±0.418
F7	97±0.921	0.507±0.03	27±0.5
F8	96.65±0.976	0.529±0.006	28.8±0.57

All values expressed as mean± S.D, n=3

The dissolution data is shown in figure 3.The drug release followed first order kinetics (table 5) as the graph drawn for log % undissolved verses time is linear(figure 4). The Higuchi model indicates that the process of drug release is through diffusion pathway. All formulations showed diffusion coefficient (n > 1) indicating Case II transport following swelling controlled drug release.

Table 4: Evaluation of Rosiglitazone floating tablets

Formulation Code	buoyancy lag time (secs)	t_{50} (hrs)	Drug release at 16 hrs	Swelling Index (%)					
				Time (hrs)					
				0	1	2	3	4	5
F1	56	6.21	92.88	0	29.9	43.72	54.02	70.35	77.89
F2	65	6.55	89.05	0	30.69	44.55	54.95	70.79	78.47
F3	72	7.20	84.52	0	30.35	44.03	54.48	70.65	78.11
F4	59	6.94	86.78	0	28	41.25	52	67.25	76
F5	76	7.46	82.48	0	31.92	46.13	56.61	73.82	81.3
F6	55	6.76	88.14	0	31.25	45.25	56	72.75	80
F7	62	6.68	89.26	0	30.83	45.11	55.89	72.43	79.7
F8	68	6.49	90.17	0	32.67	46.88	57.6	75.81	84.04

Fig.2: Swelling index of formulations

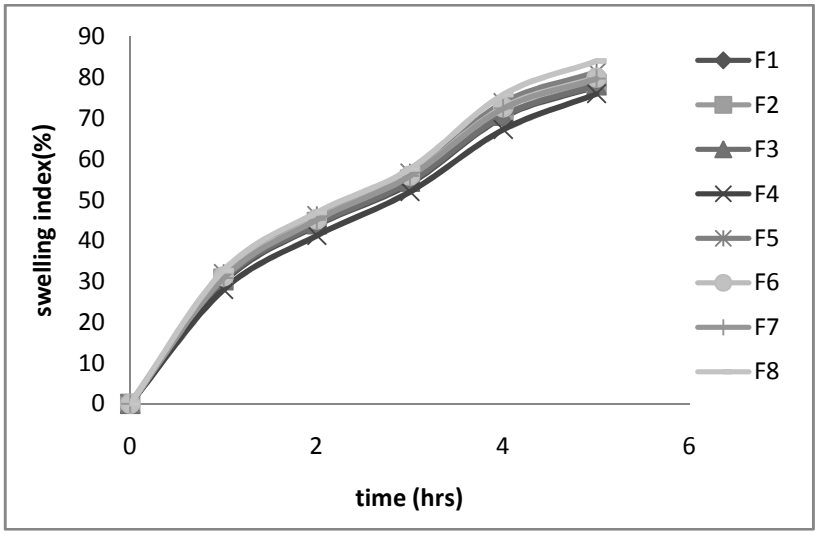


Fig.3: Comparative Invitro drug release profiles of formulations (F1-F8)

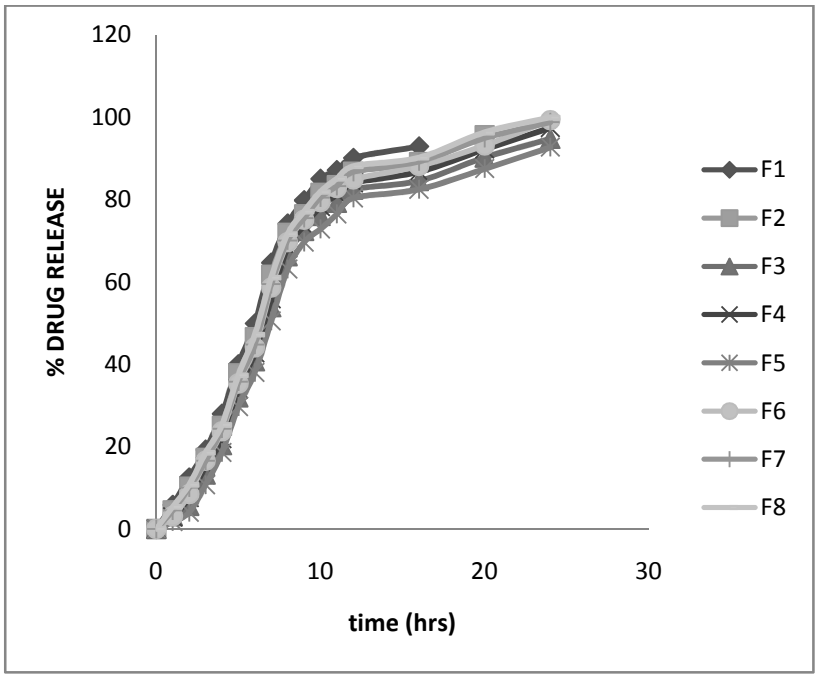


Fig 4: First order plots for Rosiglitazone maleate bi layered formulations F1 to F8

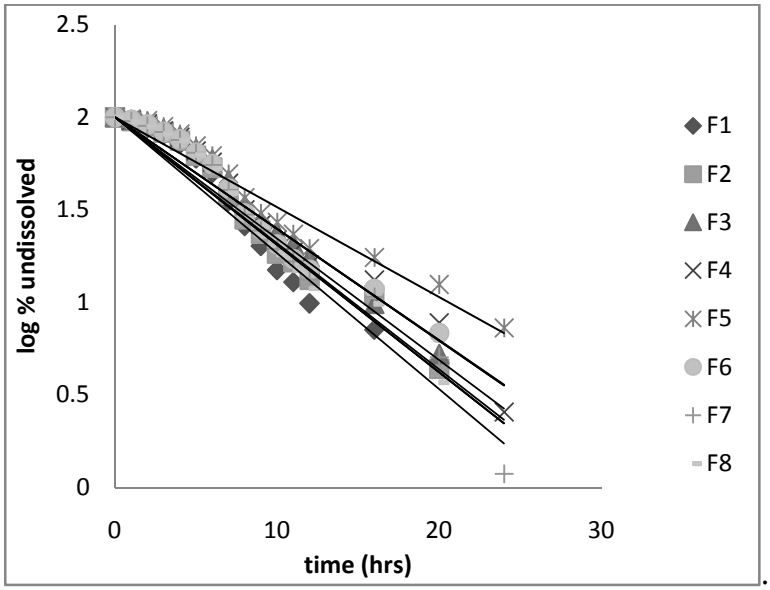


Table 5: Kinetic values obtained from different plots of F1- F8

Formulation Code	Zero order plot		First order plot			Higuchi plot	Korsemeyer Peppa's plot	
	R^2	Zero order rate constant K_0 ($mg.h^{-1}$)	R^2	n	First order rate constant K_1 (h^{-1})	R^2	R^2	n
F1	0.9126	7.07	0.9620	0.0845	0.195	0.9114	0.8889	1.3967
F2	0.8475	5.61	0.9703	0.0725	0.167	0.9043	0.8945	1.3552
F3	0.807	4.52	0.9642	0.0567	0.131	0.8912	0.9079	1.3615
F4	0.8091	4.58	0.9716	0.0661	0.152	0.8976	0.9030	1.3471
F5	0.8139	4.47	0.9568	0.0512	0.118	0.8892	0.9231	1.4610
F6	0.8074	4.61	0.9360	0.0793	0.183	0.9005	0.8951	1.3284
F7	0.8052	4.62	0.9709	0.0776	0.179	0.9007	0.8802	1.2721
F8	0.8007	4.63	0.8483	0.1107	0.255	0.9019	0.8659	1.2423

CONCLUSION

In this approach, GI residence time is prolonged because of floating behaviour coupled with bio adhesion and thus provides a convenient dosage form of Rosiglitazone maleate.

Acknowledgements
The authors are thankful to Bactolac Formulations, Hyderabad for providing the adequate laboratories facilities in the execution of this work.

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