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Formulation and *in vitro* evaluation of sustained release floating matrix tablet of Rosiglitazone Maleate

Krishna Mohan Chinnala* [1]

Rabi Narayan Panigrahy[1]

Ramesh Bantu[2]

Gowtham Reddy Kallem[2]

[1]Department of Pharmaceutics, School of Pharmacy, Nalla Narasimha Reddy Education Society's Group of Institutions, Chowdariguda, Ghatkesar, Ranga Reddy, Andhra Pradesh, INDIA -500088.
[2]Department of Pharmaceutics, St. John College of Pharmacy, Yellapur, Hasanparthy, Warangal, Andhra Pradesh, INDIA-506 371.

Corresponding Authors:
Dr. Krishna Mohan Chinnala
Dean and Professor School of Pharmacy, Nalla Narasimha Reddy Education Society's Group of Institutions, Chowdariguda, Ghatkesar, Ranga Reddy, Andhra Pradesh, INDIA -500088.
Phone: +91 984 824 9091
E-Mail: drchinnala@gmail.com

Abstract:
The present study involves formulation and evaluation of sustained release floating tablet using Rosiglitazone maleate as a model anti-diabetic drug. Endeavors with respect to floating mechanism are inculcated in the formulation to achieve longer stay of tablet in stomach, which happens to the better site of absorption for the selected drug. Preformulation studies involving organoleptic, bulk density, angle of repose, tapped density, compressibility index, Hausner's ratio, melting point range, pH and solubility were carried out as per IP specifications. Drug excipients compatibilities were carried out physical evaluation and FTIR, which showed no significant change in any way to the mixture. Different grades of HPMC viz, E4M, E15M, K100M were utilized in the trails. All the physical evaluations and preformulation studies were carried out on all the three different polymers utilized. All the formulations exhibited values within the acceptable range. Rosiglitazone tablets were evaluated for weight variations, hardness, friability, thickness, and buoyancy studies. Release studies were carried out in 0.1 N HCL, for 12 hours. Results indicated that formulation F4, gave 93.78% release up to 12 hrs, which is formulated with E15M alone. Assay was carried out for formulation F4 and was found to be 99.23%. The mechanism of drug release form matrix tablets follows Non-Fickian release (Diffusion and Swelling). Remaining formulations gave fluctuating release profiles. The formulation F4 was considered to be better among the trails accomplished.

Keywords: Rosiglitazone, floating, anti-diabetic, FT – IR, buoyancy studies, Non-Fickian release.

Introduction

Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It also has applications for local drug delivery to the stomach and proximal small intestine. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.[1, 2]

One of the most feasible approaches for achieving a prolonged and predictable drug delivery profiles in gastrointestinal tract is to control the gastric residence time (GRT) using gastroretentive dosage forms (GRDF) that offer a new and better option for drug therapy. Dosage forms that can be retained in stomach are called 'gastro retentive drug delivery systems' (GRDDS) [3]. GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site thus ensuring its optimal

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bioavailability. Several approaches have been attempted in the preparation of gastro-retentive drug delivery systems. This include Floating systems, Bioadhesive systems, Swellable systems, High density systems and Modified-shape systems. Floating drug delivery system have a bulk density less than gastric fluids (less than 1.004 g/ml) and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of fluctuations in plasma drug concentration. The floating sustained release dosage forms present most of the characteristics of hydrophilic matrices and are known as 'hydrodynamically balanced systems' ('HBS'), since they are able to maintain their low apparent density while the polymer hydrates and builds a gelled barrier at the outer surface. The drug is released progressively from the swollen matrix, as in the case of conventional hydrophilic matrices. These forms are expected to remain buoyant on the gastric contents without affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric contents [4]. Melt granulation is one of the most widely applied processing techniques in the array of pharmaceutical manufacturing operations. Melt granulation process is currently applied in the pharmaceutical field for the manufacture of variety of dosage forms and formulate such as immediate release and sustained release pellets, granules and tablets. Diabetes mellitus Type-II (formerly called non-insulin-dependent diabetes mellitus (NIDDM) or adult - onset diabetes) is a metabolic disorder which is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency. Rosiglitazone maleate (±)-5-[[4-[2-(methyl-2-pyridinylamino) ethoxy]-phenyl] methyl]-2, 4-thiazolidinedione, (Z)-2-butenedioate is an oral antidiabetic agent, which acts primarily by increasing insulin sensitivity. It is effective only in the presence of insulin. It decreases insulin resistance at peripheral sites and in the liver. This results in insulin-dependent glucose disposal and reduced hepatic glucose output. 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 [5, 6 and 7]

Materials and Methods

Rosiglitazone maleate was obtained as gift sample from Syskem Pharmocrats, Solan, HPMC E4M was gifts from Glukem Pharmaceutical, Hyderabad, HPMC E15M and HPMC K100M (Suzikem Drugs Pvt. Ltd., Hyderabad, India) were obtained from commercial sources. Sodium Bicarbonate was gifts from Fine Chem. industries. All other reagents and chemicals used were of analytical reagent grade.

Formulation of Rosiglitazone maleate Floating Tablets [8]

Rosiglitazone maleate Floating Tablets were prepared by 'Melt granulation method'. The ingredients were accurately weighed. Rosiglitazone Maleate, HPMC E4, HPMC E15, HPMC K100 were Sieved through mesh no. 80. White bees wax was melted in a china dish. Added Rosiglitazone maleate drug on molten mass and stirred well to mix. Then added HPMC polymers, sodium bicarbonate and lactose and mix it well. Then the mass was allowed to cool to

room temperature and then scrapped from china dish. The coherent mass was passed through sieve no. 20. The resulting granules were mixed with magnesium stearate and talc. The lubricated granules were compressed into tablets using 12 mm standard concave punch with 16 station single rotary Cadmach machine and keeping average weight of 400 mg. The compressed tablets of each type of polymer were then evaluated for tablet characteristics such as thickness, weight variation and friability. Compositions Of various formulations are shown in Table 1.

Table 1: Formulation of Rosiglitazone maleate Floating Tablets

Ingredients/ Batches	F1	F2	F3	F4	F5	F6	F7	F8	F9
Rosiglitazone Maleate	100	100	100	100	100	100	100	100	100
HPMC E4M	80	100	120	-	-	-	-	-	-
HPMC E15M	-	-	-	80	100	120	-	-	-
HPMC K100M	-	-	-	-	-	-	80	100	120
Bees wax	100	100	100	100	100	100	100	100	100
NaHCO3	50	50	50	50	50	50	50	50	50
Lactose	60	40	20	60	40	20	60	40	20
Talc	5	5	5	5	5	5	5	5	5
Mg. stearate	5	5	5	5	5	5	5	5	5
Total	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**

Characterization of Drug & Polymers

Micromeritic Evaluation of drug & polymers [9]

Bulk density & Tapped density

5gm of drug & polymers weighed separately & poured in a 50 ml measuring cylinder, the fluff volume was noted then tapped for 100 times from a uniform height and the tapped volume were determined.

Density = Mass/ volume, Bulk density = 5gm/ bulk volume, Tap density =5gm/ tapped volume

Carr's Index (% Compressibility)

Flow ability of the formulation can be determined by using following equation

Carr's Index= [(Tapped Density – Bulk Density) / Tapped Density] x 100

Hausner's Ratio

It is calculated by using formula

Hausner's Ratio = Tapped Density / Bulk Density

Angle of repose

Angle of repose has been defined as the acute angle possible between the surface of pile and horizontal plane. The angle of repose was determined by the funnel method. The drug & polymers were allowed to flow out of the funnel orifice on a plane Paper kept on the horizontal surface. This forms a pile on the paper. The angle of repose was calculated by substituting the values of the base radius 'r' and pile height 'h' in the following equation

$\tan \theta = h/r$

Hence, $\theta = \tan^{-1} h/r$

Where, θ = angle of repose, h = height of the cone r = radius of the cone base

Fourier Transform Infrared Spectroscopy (FT-IR)

The drug & polymers were characterized by Fourier transformed infrared spectroscopic analysis (FT-IR), to ascertain for any interaction between the drug and the polymers used and to confirm the encapsulation of the drug with in polymer matrix. For this purpose, spectra of the pure drug, and mixture containing the drug and polymer was taken. An FT-IR spectrometer was

used for the analysis in the frequency range between 4000 to 400 cm^{1}.

Evaluation of Rosiglitazone maleate Floating Tablets [9, 10]

Micromeritic characterization of precompressed granules

The characteristic parameters of the precompressed granules were evaluated. The angle of repose and flow rate were determined by the funnel method. The bulk density and tapped density were determined by the cylinder method and Carr's index was calculated using the following equation

Carr's index = $Df - D0/Df \times 100$

Where,

Df= Poured bulk or bulk density,

$D0$ = Tapped or consolidated bulk density.

The results are given in Table 3

Weight Variation

The weight variation test was run by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weight to the average. The tablets meet the USP test if no more than 2 tablets are the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Friability

The laboratory friability tester is known as the Roche friabilator. Friabilator subjects a number of tablets to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm, dropping the tablets a distance of six inches with each revolution. Normally, a pre-weighed tablet sample is placed in the friabilator, which was then operated for 100 revolutions. The tablets are then dusted and reweighed. Conventional compressed tablets that lose less than 0.5 to 1.0% of their weight are generally considered acceptable.

Hardness

Tablet requires certain amount of strength or hardness to withstand mechanical shock of handling in manufacture, packaging and shipping. The hardness of the tablet was measured by Monsanto hardness tester. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger is placed in contact with the tablet and a zero reading was taken. The upper plunger is then forced against a spring by turning threaded bolt until the tablet fractures.

Thickness

Thicknesses of the 10 tablets were measure by using Screw-gauze.

Drug content

100mg of Rosiglitazone maleate containing formulation (400mg) dissolved in 0.1 N HCl to produced 100ml of solution. 10ml of solution was then diluted to 100ml, by using distilled water and then analyzed in Double beam spectrophotometer at 318 nm.

Floating time studies

The buoyancy lag-time of the tablets was studied at 37 ± 0.5°C, in 100 ml 0.1N HCL. The time required for the tablet to rise to the surface and float was taken as the buoyancy lag-time. The duration of floating is known as floating time.

In vitro dissolution studies [11, 12]

The release rate of Rosiglitazone maleate from floating matrix tablets was determined using USP dissolution testing apparatus II (Paddle type). The dissolution test was performed using 900 ml 0.1N HCL, at 37 ± 0.5°C and 75 rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 h, and the samples were replaced with fresh dissolution medium. The samples were passed through Whatman's filter

paper and the absorbance of these solutions was measured at318 nm.

Data analysis [13, 14, 15 and 16]

To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into zero order, first order, Higuchi matrix and Korsemeyer-peppas model, based on the r value the best fit model was selected.

RESULTS AND DISCUSSION

Micromeritic Evaluation of drug & polymers

Rosiglitazone Maleate Floating Tablets were mainly prepared by using different polymers like HPMC E4M, HPMC E15M and HPMC K100M in combination (Table 1). The tablets were fabricated using melt granulation technique. The Micromeritic property of drug and polymers were characterized with respect to the angle of repose, bulk density, tap density, hausner's ratio and Carr's index (Table 2).the Micromeritic property of both drug & polymers were comply with pharmacopoeial specifications.

Table 2: Micromeritic characterization of drug and polymers

Parameters/Polymers	Rosiglitazone maleate	HPMC E4M	HPMC E15M	HPMC K100M
Loose bulk density(g/cm³)	0.23±0.03	0.217±0.021	0.304±0.020	0.454±0.021
Tapped density(g/cm³)	0.31±0.03	0.312±0.0189	0.478±0.029	0.666±0.021
Carr's Index	25.80%	30.60	36.40	31.98
Hausner's ratio	1.34	1.43	1.57	1.46
Angle of repose	33°.85''±0.4	18±0.6	17±0.3	16±0.8

Each sample was analyzed in triplicate Mean ± S.D (n = 3).

FTIR Spectroscopy

Drug- excipients interactions play a vital role with respect to release of drug from the formulation amongst others. FTIR techniques have been used here to study the physical and chemical interaction between drug and excipients used. In the present study, it has been observed that there is no chemical interaction between Rosiglitazone maleate and the polymers used. From the figures 1.1 and 1.2 it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers.

Figure 1.1: FT-IR Graph of Rosiglitazone Maleate

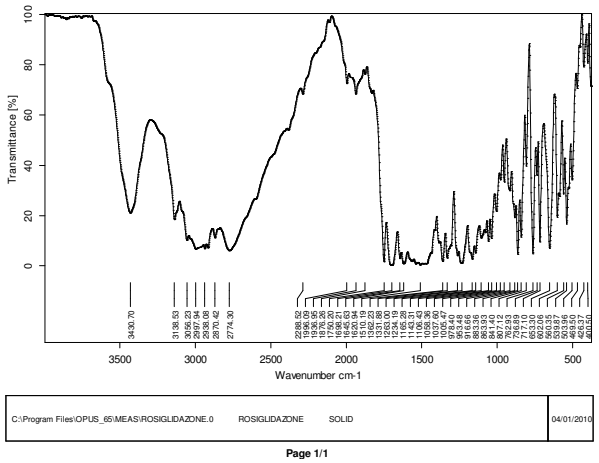
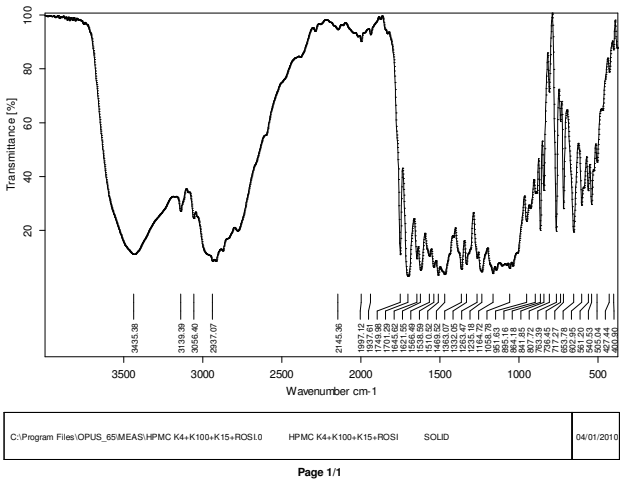


Figure 1.2: FT-IR Graph of Mixture of Rosiglitazone + HPMC E4M + HPMC E15M + HPMC K100M



Micromeritic Evaluation of Precompressed granules

The Micromeritic properties of Precompressed granules were characterized with respect to the angle of repose, bulk density, tap density and Carr's index (Table 3). The angle of repose for the formulated blend F1-F9 was found to be in the range $24^0.53'$ to $27^0.03'$ shows good flow property. Compressibility index for the formulations F1-F9 found between 15.36% to 18.03% indicating the powder blend has the required flow property for compression.

Table 3: Evaluation of Granules

Batch. No	Angle of Repose (^{0})	Bulk Density(g/ml)	Tapped bulk density(g/ml)	Carr's index (%)	Hausner's Ratio
F1	25° 48'	0.2973	0.3608	17.59	1.21
F2	26° 63'	0.2856	0.3444	17.03	1.20
F3	24° 53'	0.2876	0.3398	15.36	1.18
F4	26°34'	0.2899	0.3435	15.60	1.18
F5	26° 54'	0.2669	0.3213	16.93	1.20
F6	26° 62'	0.2778	0.3322	16.37	1.19
F7	27° 03'	0.2549	0.3110	18.03	1.22
F8	26° 77'	0.2768	0.3376	18.01	1.21
F9	25° 54'	0.2858	0.3453	17.21	1.20

Physical Evaluation of tablets

The formulated tablets were subjected for various evaluation parameters like hardness, thickness, weight variation, friability, buoyancy time and total Buoyancy time. Our experimental results (Table 4) revealed that all the formulated tablets were of good quality with regard to hardness (3- 4 kg/cm2), friability (below 1%) and thickness (3.05 to 3.87 mm). The weight variation of the tablet in the range of ± 1.56 % to ± 2.33 % (below 5%) complying with pharmacopoeial specification. From the results all batches shows good buoyancy (up to 12 hours).

Table 4: Evaluation of Rosiglitazone Maleate Floating Tablets

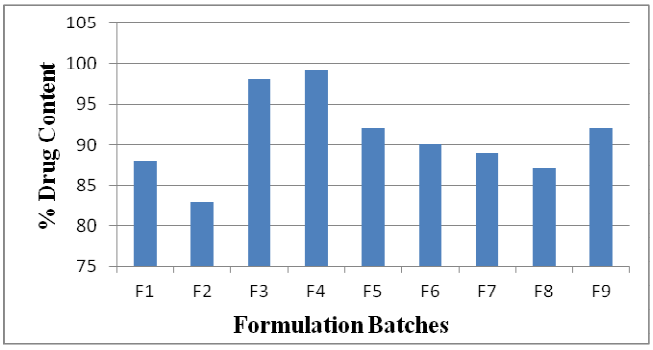
Formulation Batches	Hardness (kg/cm^2)	Thickness (mm)	Weight variation	Friability (%)	Buoyancy lag time(sec)	Total Buoyancy time(hours)
F1	3.4±0.25	3.59±0.04	±1.98	0.18	105	12
F2	3.5±0.13	3.67±0.08	±1.99	0.23	265	8
F3	3.8±0.23	3.78±0.03	±2.32	0.19	378	10
F4	3.5±0.12	3.28±0.06	±1.78	0.23	123	11
F5	3.9±0.20	3.42±0.06	±2.10	0.25	231	9
F6	3.7±0.05	3.52±0.03	±2.19	0.23	287	12
F7	3.4±0.25	3.05±0.04	±2.33	0.21	156	11
F8	3.6±0.10	3.72±0.05	±1.65	0.18	298	12
F9	3.8±0.16	3.87±0.15	±1.56	0.21	398	13

Each sample was analyzed in triplicate Mean ± S.D (*n* = 3).

Drug Content

Drug content was determined by using equation prepared from the Calibration curve of the Rosiglitazone maleate in 0.1 N HCl and calculated by using equation (**Y=0.032X+0.007).** Formulation F4 (HPMC E15M) shows highest percentage of drug content i.e. 99.23% as compared to other formulations. (Figure 2)

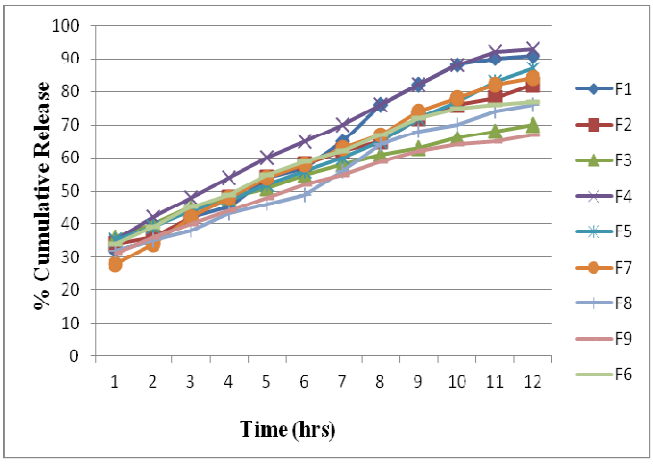
Figure 2: Percentage Drug content for Rosiglitazone maleate floating matrix tablet



In vitro dissolution studies[6, 7]

From the *in vitro* dissolution study of all formulations (F1-F9), formulation F4 showed release around 93.78% of drug at the end of 12 hours (Figure 3).Therefore for sustained release formulation F4 chosen as the best formulation.

Figure 3: *In vitro* dissolution studies of Rosiglitazone Maleate floating matrix tablets



Data analysis

Kinetic models describe drug release from immediate and modified release dosage forms. To predict the mechanism of diffusional release, equation $Mt / M\infty = kt^{n}$ was used. Different kinetic was applied to interpret the release rate of Rosiglitazone maleate from floating matrix tablets. The regression coefficient values and n values (Table 5) Showed that the drug releases follow Non-Fickian release. (Diffusion and Swelling).

Figure 4.1: ZERO ORDER

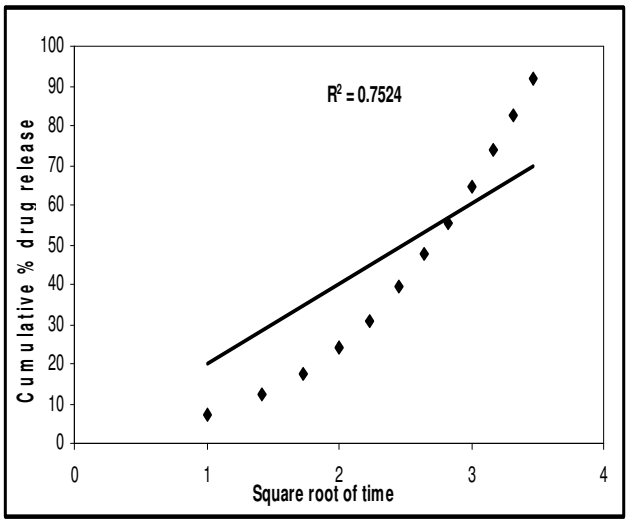


Figure 4.2: FIRST ORDER

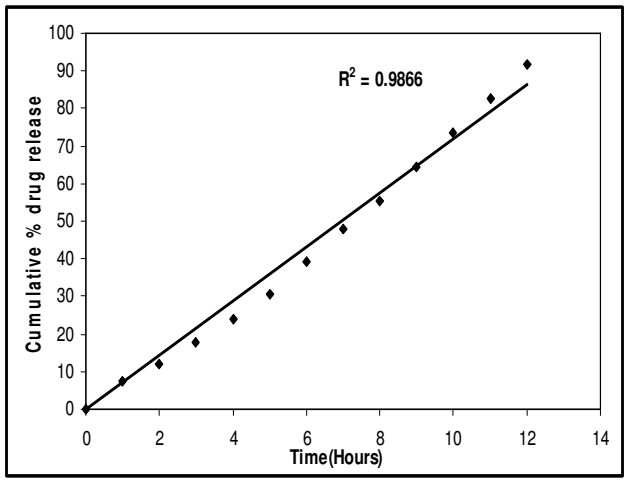


Figure 4.3: HIGUCHI MODEL

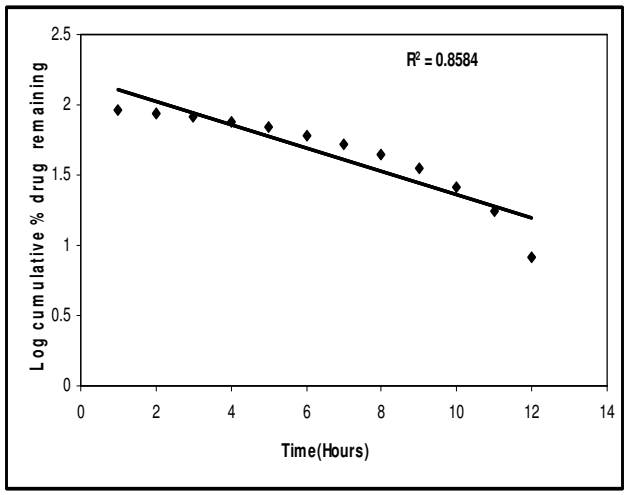


Figure 4.4: KORSMEYER-PEPPAS MODEL

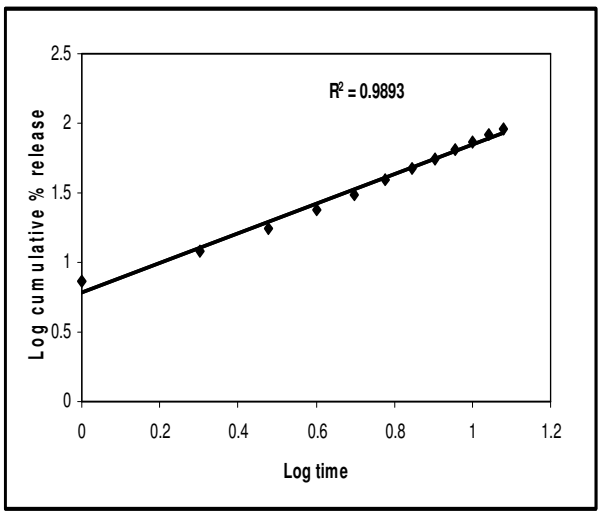


Table 5: Regression coefficient of F4

Formulation	Regression coefficient (R^2) value			
	Zero-order	First order	Higuchi	Korsmeyer - Peppas
Rosiglitazone maleate	0.9866	0.8584	0.7524	0.9893

Conclusion

Observations of all formulations for physical characterization had shown that, all of them comply with the specifications of official pharmacopoeia and/or standard reference. Drug & excipients compatibilities were carried out by using FTIR, which showed no significant change in any way to the mixture. Different grades of HPMC viz, E4M, E15M, K100M were utilized in the trails. All the physical evaluations and preformulation studies were carried out on all the three different polymers utilized. All the formulations exhibited values within the acceptable range. Tablets were evaluated for weight variations, hardness, friability, thickness, and buoyancy studies. Release studies were carried out in 0.1 N HCL, for 12 hours. Results indicated that formulation F4, gave 93.78% release up to 12 hrs, which is formulated with E15M alone. Assay was carried out for formulation F4 and was found to be 99.23%. The mechanism of drug release from matrix tablets follows Non-Fickian release (Diffusion and Swelling). Remaining formulations gave fluctuating release profiles. From the above research work it can be concluded that HPMC E15M is the best suitable polymer for the formulation of Rosiglitazone maleate floating matrix tablet.

References

1) Shah S.H., Patel N.V. Stomach specific floating drug delivery system: A review. *International Journal of Pharm Tech Research*-2009;3;623-633.
2) Shweta Arora, Javed Ali, Alka Ahuja, Roop K.Khar And Sanjula Baboota; Floating drug delivery systems: A review., *AAPS Pharm Sci Tech* 2005,6(3), article 47, ppE372-390.
3) Kumar S., Pandey M, Novel sustained release Gastroretentive floating matrix tablet of Acyclovir. *j.pharm.res*. 2009, 2(4):717-722.
4) Ms. Julan. U. Desai Floating Drug Delivery Systems: An approach to Gastro retention. www.pharma info.net.
5) J. E. F. Reynolds.Director of the Council of Royal Pharmaceutical Society of Great Britain, *Martindale-the extra Pharmacopoeia* 2005, 34: 345.
6) G. K. McEvoy. AHFS Drug Information. *Authority of the board of the American Society of the Health-System Pharmacists*, 2004, 3055-3058.
7) M. C. Chapel Sky, K. Thompson-culkin, A. K. Miller. Pharmacokinetics of rosiglitazone in patients with varying degrees of renal insufficiency. *J. Clin. Pharmacol*, 2003, 43: 252-259.
8) Patidar HC, P. D. Chaudhari., Formulation and in *vitro* evaluation of oral floating tablets of atorvostatin calcium by Melt Granulation Technique: A Review, *International Journal of Pharmaceutics* (2009)1(4),492-495.

9) Remington, *The science and practice of pharmacy*, 19th Edition, vol. I, Page No. 1669-1670.
10) Government of India ministry of health and family welfare. *The Pharmacopoeia of India*. Controller of publication, 1996.
11) Gambhire M N, Ambade K W, Kurmi S D, Kadam V J, Jadhav K R, Development and *in vitro* evaluation of an oral floating matrix tablet formulation of Diltiazem hydrochloride, *AAPSPharm. SciTech* 2007; 8(3): article 73, 1-16
12) Patel F V, Patel M N, Yeole G P, Studies on formulation and evaluation of ranitidine floating tablets, *Indian J, Pharm. Sci*., 2005, 67(6), 703-709.
13) Higuchi.T, *Journal of Pharma Sciences*, 52, 1963, 1145-1149.
14) Higuchi W. I., Stenhle R. G., *Journal of Pharm. Sciences*, Vol. 64,1965; 265
15) Korsmeyer.R.W, Gurny.R, Doelker.E, Bur.P and Peppas .N.A. "*Int. J. of Pharmacy*", 15, 1983; 25-35.
16) Ritger P L, Peppas NA; *Journal of controlled release* 1987, 5, 23-36.

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