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Formulation and *in vitro* Evaluation of Gastroretentive Rosiglitazone maleate Floating Tablets

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Abstract

The present study performed by Formulation and Evaluation of Floating Tablets of Rosiglitazone maleate as a model drug for prolongation of gastric residence time. Floating effervescent tablets were formulated with various materials like hydroxyl propyl methyl cellulose (HPMC) K4, K15, K100 at varying concentrations were used for its gel forming release controlling properties, sodium bicarbonate act as a effervescent agent and hydrophobic meltable material like bees wax was used. The tablets were prepared by melt granulation technique and the prepared tablets remained buoyant for more than 12 hours in the released medium. The variant proportion of the polymers HPMC K4, K15, K100 showed significant difference in the release rate, buoyancy and lag of the tablet.

Keywords: Floating tablet, Rosiglitazone, Melt-granulation, HPMC.

1. INTRODUCTION

During the last three decade many studies have been performed concerning the sustained release dosage form of drugs, which have aimed at the prolongation of gastric retention time (GRT). The GRT has been reported to be from 2 to 6 hours[1] in humans in the fed state. There are various approaches[1-2] in the Gastroretentive system of these floating is a very best method.

Floating Drug Delivery 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.[1-2] 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 possesses most of the characteristics of hydrophilic matrices and are known as 'hydrodynamically balanced systems[1] ('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 hydrophilic matrices.

Rosiglitazone maleate (±)-5-[[4-[2-(methyl-2-pyridinylamino) ethoxy]-phenyl] methyl]-2, 4-thiazolidinedione, (Z)-2-butenedioate[3-7] is an oral antidiabetic agent, which acts primarily by increasing insulin sensitivity.[5] It decreases insulin resistance at peripheral sites and in the liver.[5-6] This results in insulin-dependent glucose disposal and reduced hepatic glucose output. The half-life of Rosiglitazone maleate[5-7] is 3-4 hours and it reaches a peak plasma concentration after 1 h. It is highly soluble[5,7] in 0.1/l mol HCl (11.803 mg/ml) and its solubility decreases with increasing pH over the physiological range.[7]

2. MATERIALS AND METHODS

2.1. Materials

Rosiglitazone maleate was received as a gift sample from Sooriyan pharmaceuticals, Chennai, HPMC all grades were received as a gift from the Burgeon pharmaceuticals, Chennai, and other ingredients used were of analytical grade.

2.2. Methods

2.2.1. Dose calculation

For sustained drug release up to 12 hours, 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

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

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.

For rosiglitazone maleate

$$Dt = 2\ [1+ (0.693 \times 12)/3.5)]$$

Dt = 6.752 mg rosiglitazone and 8.945 mg rosiglitazone maleate is equivalent to 6.75 mg rosiglitazone.[8]

2.2.2. Preparation of Floating tablets by Melt granulation technique

Required quantity (Table 1.) of bees wax was taken in a large china dish over a water bath for melting the wax. The Rosiglitazone maleate was added to the molten mass and mixed well. Then previously prepared geometric mixture of HPMC, sodium bicarbonate, lactose was added to the molten mass mixture and stirred well to mix. Then the coherent mass is removed from the water bath and subjected to scrapping until it attained from room temperature. The coherent mass was passed through sieve no.24. The granules were collected and mixed with talc and magnesium stearate. The lubricated blend was compressed into tablets using 9mm standard concave punch with 16 station rotary cadmach machine.

2.2.3. Evaluation of granule

2.2.3.1. Angle of repose

Flow property of the granules was evaluated by determining the angle of repose and the compressibility index. Static angle of repose was measured according to fixed funnel method and free standing cone method (Banker and Anderson). The angle of repose was calculated using the equation, $\tan \theta = h/r$ Where, θ is the angle of repose.

2.2.3.2. Bulk density

Loose bulk density (LBD) and Tapped bulk density (TBD) were determined for the prepared granules. LBD and TBD was calculated (Table. No: 2) using the formula,

LBD = Wt of Powder / Vol. of Powder

TBD = Wt of Powder / Tapped Vol. of Powder

2.2.3.3. Compressibility Index and Hausner ratio

Carr's Compressibility Index for the prepared granules was determined by the equation,

Carr's Index (%) = TBD – LBD/TBD x 100

Hausner Ratio = Vb/Vt

Where,

V_b = initial or bulk volume

V_t = final or tapped volume

2.2.4. Evaluation of Tablets

Tablets from all the eight formulations were evaluated for its various properties like thickness using vernier calipers, hardness by using Monsanto hardness tester (Cadmach), friability by using Roche Friabilator, and weight variation by using an electronic balance (Anamed).

2.2.4.1. *In vitro* buoyancy studies

In vitro buoyancy was determined by floating lag time as per the method described by Rosa *et al*. The tablets were placed in a 100 ml glass beaker containing 0.1M HCL as per IP. The time required for the tablet to rise to the surface and float was

determined as floating lag time. The total floating time also determined.

Table 1. Formulation.

INGREDIENTS (in mg)	FORMULATION BATCHES							
	F1	F2	F3	F4	F5	F6	F7	F8
Rosiglitazone Maleate	9	9	9	9	9	9	9	9
HPMC K4M	0	30	0	0	30	30	0	30
HPMC K15M	0	0	30	0	30	0	30	30
HPMC K100M	0	0	0	30	0	30	30	30
Sodium bicarbonate	25	25	25	25	25	25	25	25
Bees wax	30	30	30	30	30	30	30	30
Lactose	124	94	94	94	64	64	64	34
Magnesium stearate	6	6	6	6	6	6	6	6
Talc	6	6	6	6	6	6	6	6
Average weight	200	200	200	200	200	200	200	200

2.2.4.2. *In vitro* dissolution studies

The *in vitro* dissolution study of Rosiglitazone maleate tablets was performed using USP XXII Dissolution test apparatus employing paddle stirrer (75 rpm) at 37±0.5^{0}C using simulated 0.1M HCL (900 ml) as a dissolution media. At the predetermined time intervals, 10 ml samples were withdrawn, diluted, and assayed at 285 nm using a Syntronics UV/Vis double beam spectrophotometer (model:2202). The Cumulative percentage drug release was calculated using an equation obtained from the calibration curve.

2.2.4.3. Release Kinetics Analysis

The drug release data were fitted to various models like Higuchi's model (cumulative percent release against square root to time), Zero order model (cumulative percent release against time), First order model (log cumulative percent release against time) and Korsmeyer's peppas model (log cumulative percent release against log time) kinetics to know the release mechanism.

3. RESULTS AND DISCUSSION

All the formulations showed good flow properties. Angle of repose ranged from 24^0.77' to 27^0.74' compressibility index ranged from 38% to 16.13% and hausner ratio ranged from 1.11% to 1.22%. The bulk density and tapped density ranges from 0.2721 to 0.2925 and 0.3177 to 0.3503 respectively (Table 2.).

From the results of angle of repose and hausner ratio shows good flow property of granules and compressibility values shows the granules has the required flow property for compression.

The shape of the tablets of all eight formulations remained circular with no visible cracks. The thickness ranged from 3.42±0.01mm to 3.54±0.02mm, the weight variation of 20 tablets ranged from ± 1.44 % to ± 2.56 % (below 7.5%) complying with pharmacopoeial specification. The hardness of the tablets ranging from 3.5±0.05 to 3.9±0.20 indicating a satisfactory mechanical strength. The percentage friability of the all batch tablets ranging from of 0.18 % to 0.28% **(**below 1%) complying with pharmacopoeial specifications (Table 3.).

3.1. *In vitro* Buoyancy studies

From all the eight formulations, F1, F4, F7, F8 exhibited satisfactory floatation ability and remained buoyant for more than 12 hours in dissolution medium (0.1 M

HCL). The buoyancy lag-time of tablets depends on the amount of sodium bicarbonate involved in CO_2 formation. For a floating system, the ideal matrix should be highly permeable to dissolution media in order to initiate rapid generation of CO_2, and allow release of CO_2 to promote floating. Formulations F2 to F8 showed buoyancy lag-times ranging from 41 to 112 sec (Table 4.).These results indicate that the buoyancy lag-time was satisfactory when using 25 mg of sodium bicarbonate.

3.2. *In vitro* dissolution studies

The pharmacokinetic parameters of rosiglitazone were used to calculate a theoretical drug release profile for 12 hour dosage form. The *In Vitro* drug Release studies revealed that formulations F1, F4, F7, F8 Shows release of 67.91%, 62.32%, 91.78%, 73.19% respectively. The formulation F1, F2, F8 shows release of 67.91- 73.19% at the end of 12 hours these reveals that the formulations shows very poor release (Table 5.). The best formulation is selected as F7 because of its best release at the end of the 12 hours of 91.78%, the lag time of it is 85 secs.

Table 2. Evaluations of Granules

Batch. No	Angle of Repose(^{0})	Bulk Density(g/ml)	Tapped bulk density(g/ml)	Carr's index (%)	Huasner Ratio
F1	26 ^{o} 32'	0.2891	0.3503	17. 47	1.21
F2	25^o 64'	0.2768	0.3394	18.44	1.22
F3	27^o 03'	0.2924	0.3321	11.94	1.13
F4	26^{o}12'	0.2965	0.3446	13.96	1.16
F5	26^o 62'	0.2862	0.3420	16.31	1.19
F6	27^{o}74'	0.2871	0.3318	13.47	1.15
F7	24 ^{o} 77'	0.2721	0.3242	16.07	1.19
F8	26 ^{o} 56'	0.2847	0.3177	10.38	1.11

Table 3. Evaluations of Rosiglitazone Floating Tablets.

Batch. No	Weight Variation (%)	Thickness (mm)	Friability (%)	Hardness (Kg/cm^2)
F1	±1.52	3.53±0.02	0.21	3.7±0.20
F2	±2.37	3.44±0.03	0.24	3.6±0.10
F3	±1.44	3.56±0.01	0.20	3.5±0.15
F4	±1.86	3.54±0.02	0.18	3.6±0.05
F5	±2.56	3.49±0.03	0.28	3.9±0.20
F6	±2.13	3.52±0.02	0.27	3.8±0.15
F7	±2.25	3.45±0.01	0.23	3.6±0.15
F8	±1.93	3.42±0.02	0.19	3.7±0.20

Table 4. Buoyancy Lag time, Total floating time

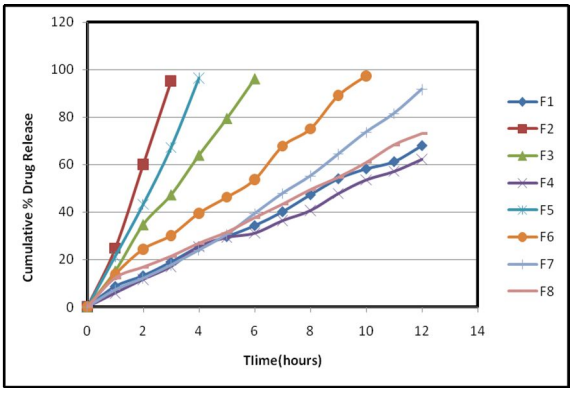
Batch. No	Buoyancy lag time(sec)	Total Buoyancy time(hours)
F1	575	15
F2	92	3
F3	96	6
F4	46	15
F5	112	5
F6	54	10
F7	85	12
F8	41	14

Table 5. IN-VITRO RELEASE PROFILE

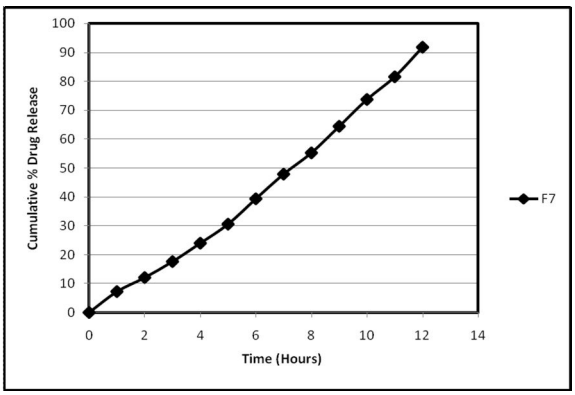
Time (h)	Cumulative Drug Release (%)							
	F1	F2	F3	F4	F5	F6	F7	F8
1	8.65±0.54	24.79±0.63	15.13±0.37	5.91±0.67	21.32±0.65	13.76±0.12	7.24±0.45	12.25±0.53
2	13.12±0.78	60.12±0.08	34.67±0.83	11.64±0.12	43.13±0.30	24.34±0.39	12.09±0.34	16.79±0.35
3	18.90±0.13	95.39±0.34	47.21±0.36	17.08±0.30	67.08±0.46	30.14±0.71	17.62±0.32	21.38±0.29
4	25.34±0.35		63.90±0.24	25.42±0.56	96.34±0.67	39.51±0.46	23.98±0.28	26.86±0.54
5	29.59±0.46		79.39±0.51	29.32±0.83		46.23±0.38	30.56±0.78	31.54±0.45
6	34.23±0.34		96.14±0.39	31.13±0.29		53.69±0.19	39.34±0.67	37.67±0.39
7	40.09±0.74			36.41±0.45		67.76±0.76	47.87±0.53	43.34±0.29
8	47.23±0.20			40.69±0.76		75.09±0.41	55.23±0.23	49.50±0.16
9	53.98±0.16			47.86±0.36		89.13±0.20	64.42±0.30	54.71±0.37
10	58.14±0.59			53.63±0.54		97.43±0.46	73.7±0.36	60.92±0.48
11	61.17±0.12			57.20±0.98			81.54±0.61	68.43±0.29
12	67.91±0.36			62.32±0.34			91.78±0.73	73.19±0.56

*n=3 (S.D)

Graph No: 1. *In-vitro* Dissolution release profiles for F1-F8 Formulations



Graph No: 2. *In-vitro* Dissolution release profiles for F7 Formulation



Graph No: 3. Zero Order Kinetic Release Model

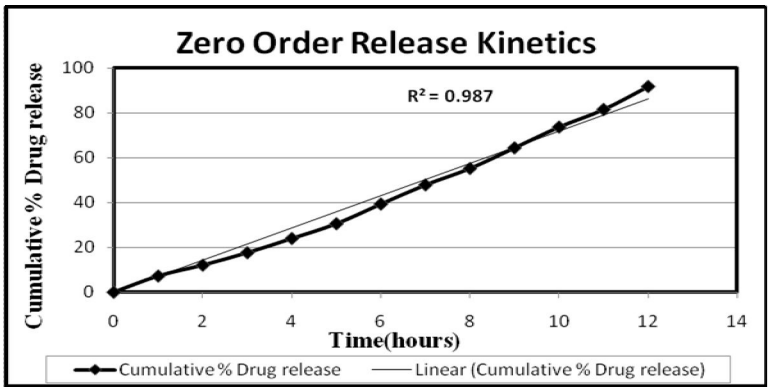


Table 6. Drug release kinetics of Formulation F7

Time(hours)	Square root of time	Log time	Cumulative % Drug release	Log cumulative % drug release	Log cumulative % Drug remaining
0	0	0	0	0	92.76
1	1	0	7.24	0.859739	87.91
2	1.4142	0.30103	12.09	1.082426	82.38
3	1.7320	0.477121	17.62	1.246006	76.02
4	2	0.60206	23.98	1.379849	69.44
5	2.2360	0.69897	30.56	1.485153	60.66
6	2.4494	0.778151	39.34	1.594834	52.13
7	2.6457	0.845098	47.87	1.680063	44.77
8	2.8284	0.90309	55.23	1.742175	35.58
9	3	0.954243	64.42	1.809021	26.3
10	3.1622	1	73.7	1.867467	17.33
11	3.3166	1.041393	81.54	1.917348	8.22
12	3.4641	1.079181	91.78	1.962748	0.8584

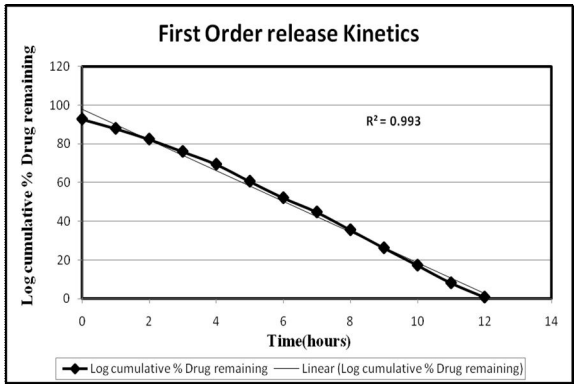
Table 7. Regression coefficient of F7

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

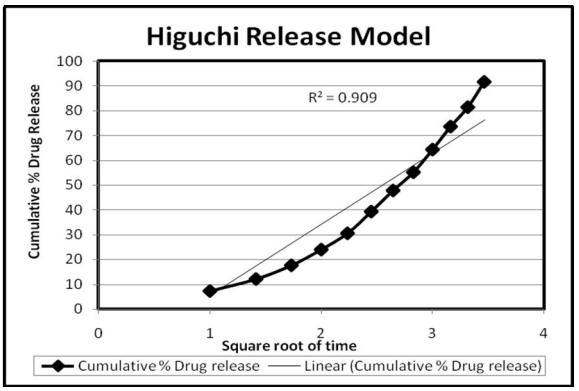
n = 0.9732

The regression coefficient values and n values show that the drug releases follow Non-Fickian release. (Diffusion and Swelling).

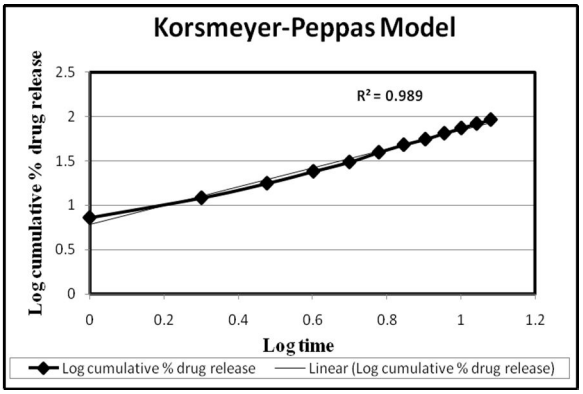
Graph No: 4. First Order Kinetic Release Model



Graph No: 5. Higuchi Kinetic Release Model



Graph No: 6. Korsmeyer-Peppas Kinetic Release Model



3.3. Drug release kinetics

To analyze the mechanism of drug release from the prepared formulation F7, the data obtained from *in vitro* release studies were subjected to Zero order, First order Higuchi's model, and Korsmeyer's model (Graph. No: 3, 4, 5, 6).

From the regression coefficient values (Table 6,7.) (R^2- 0.9893) and n values shows that the drug release of Formulation F7 follows Non-Fickian release (Diffusion and swelling).[8-9]

4. CONCLUSION

From the F1-F8 formulations F7 formulation containing HPMC K15M and K100M shows sustained release profile and releases upto 12 hours and it shows good buoyancy and total floating time. Floating tablets with sustained release characteristics offer critical advantages such as, site specificity with improved absorption and efficacy. This technology can be inculcated to various medicaments which have stomach as the major site of absorption.

Moreover, floating mechanism dosen't require any complex technology and hence, easy to adopt. Hence, it can be employed in various developmental studies based on requirement.

5. REFERENCES

1. Shah SH and Patel NV. Stomach specific floating drug delivery system: A review. **International Journal of Pharm Tech Research.** 2009; 1(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): 372-390.
3. Patidar HC. A comprehensive review on floating tablets, **www.Pharma info.net.**
4. Shinde Anilkumar J. Gastroretentive drug delivery system: An overview. **www.Pharma info.net.**
5. Rosiglitazone maleate. http://www.medscape.com/viewarticle/409783
6. Rosiglitazone maleate. http://www.drugbank.ca/drugs/DB00412
7. Rosiglitazone maleate. http://www.druglib.com/druginfo/avandia
8. Patel DM, Patel NM, Pandya NN and Jogan PD. Formulation and Optimization of carbamazepine floating tablets. **Indian Jornal of Pharmaceutical Sciences.** 2007; 69(6): 763-767.
9. Arun kumar N, Rani C and Mohan raj KP. Formulation and In vitro evaluation of oral Floating tablets of atorvastatin calcium. **Research J.Pharm and Tech.** 2000; 4: 492-495.