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Design and *in vitro* Evaluation of Gastroretentive Floating Drug Delivery System of Rosigilitazone Maleate

K.Viveksarathi, K.Kannan*
Department of Pharmacy, Faculty of Engineering & Technology,
Annamalai University, Annamalai Nagar-608 002, Tamil Nadu, India.
*egkkannan@yahoo.co.in

Abstract

Rosigilitazone maleate is an anti-diabetic agent is used in the management of Type-II diabetes mellitus. The present investigation concerns the development of the sustained release floating matrix tablets which are designed to exhibit a prolonged gastric residence time and controlling the drug release from the dosage form. This system is useful particularly for achieving controlled plasma level as well as improving bioavailability of the drug. The formulated floating tablets containing 10mg Rosigilitazone maleate were developed using Hydroxyl propyl methyl cellulose (HPMC) and different additives.The formulated tablets obtained by the direct compression method, followed by optimization of the evaluated parameters were employed to get the final optimized formulation. The resulting formulations indicated optimum hardness, uniform thickness, consistent weight uniformity and low friability. The formulated tablets were able to continuously float over the stimulated gastric fluid for 24hrs. The dissolution studies showed that formulations F4, F6 and F7 exhibited sustained drug release pattern. Drug release kinetics was evaluated using the krosmeyer peppas model and found to be governed by Fickian diffusion. The floating behavior of the designed tablets could be successfully combined with accurate control of the drug release patterns.

Key Words: Rosigilitazone, Floating Tablet, Gastroretention

INTRODUCTION

Rosigilitazone maleate (±)-5-[[4-[2- (methyl-2-pyridinylamino) ethoxy]-phenyl] methyl]-2, 4-thiazolidinedione, (Z)-2- butenedioate is thiazolidinedione class of oral antihyperglycemic (antidiabetic) agent used in management of type-II (non-insulin dependent) diabetes mellitus [1, 2]. Rosigilitazone maleate acts primarily by increasing insulin sensitivity in muscle and adipose tissues and reduce the insulin resistance at peripheral sites and in the liver. It improves glycemic control while reducing circulating insulin levels. The drug is highly soluble in simulated gastrointestinal fluid, but the solubility decreases with increasing the pH above 7. The absolute oral bioavailability of Rosigilitazone maleate is 99.8% with a biological half-life of 3-4hrs [1, 3, 4]. The drug is administered orally as monotherapy for 8 to 12 weeks, may be increased from 4mg to 8mg due to the insufficient glycemic control. When the dose of Rosigilitazone maleate is increased and also increased the plasma level and these results in higher incidence of dose dependent side effects such as headache, gastrointestinal disturbances, oedema, altered blood lipids and hypoglycemia[5-7]. The adverse events of Rosigilitazone maleate were reported in clinical trials of as monotherapy are anemia, edema and weight gain [8, 9].

The objective of the current investigation was to maintain the Rosigilitazone maleate at its steady state plasma concentration. So we developed gastroretentive floating drug delivery system to achieve the drug release slowly into gastrointestinal track and maintain the constant drug concentration in the serum for a prolong period of time.

The preparation of Rosigilitazone maleate floating tablets using gas forming agent (Sodium bicarbonate), swelling agent (Crospovidone), viscolyzing agent (Microcrystalline cellulose) and rate controlling polymer (Hyperomellose) alone or in combination, and other standard excipients. Floating drug delivery system using standard manufacturer process (direct compression method) and to evaluate the *In-vitro* release pattern and to predict the release behaviour of Rosigilitazone maleate from zero-order equation, first-order equation Higuchi equation and Korsmeyer-Peppas simple exponential equation models.

MATERIALS AND METHODS

Materials

Rosigilitazone maleate was received as gift sample from Unichem Laboratory, Mumbai, India. Hydroxy propyl methyl cellulose was purchased from the Dow Chemicals Company, Michigan, USA. Xanthan gum was obtained from KR&CO International Ltd, India. Sodium bicarbonate was received from Dr.PaulLohnmann, Germany. Cross povidone was supplied by Noveon, Ohid. Microcrystalline cellulose (MCC, Avicel pH 102) was obtained from Signet chemicals, Mumbai. Magnesium stearate was procured from St.Louis, Missouri. All other ingredients used throughout the study were of analytical grades and used as received.

Preparation of floating tablets

Floating tablets, each containing 10mg Rosigilitazone maleate were prepared by direct compression method. The composition of drug and other weighed ingredients proportion and their codes were mentioned in **Table I**. Drug and other ingredients were passed through sieve no. 36#. A blend of all ingredients except lubricant were mixed uniformly for 10-15 minutes. Then the blend was lubricated with magnesium stearate, which was sifted through sieve no. 44# and continued the blending up to 5 mins. The blend was compressed with the help of CDM3-16 station rotary tablet compression machine (Cadmak, Ahmadabad, India) using flat-faced punches (diameter 12mm). Formulations

containing 10mg Rosigilitazone maleate in each tablet and the total weight of the tablet are 160mg. The powder flow properties and compressibility characteristic were evaluated before going to compression. The prepared floating tablets were stored in air tight container for further study.

All figures in the parentheses represent ±SD; n is specified in each column head

Evaluation of powder blend[10]

Static angle repose (θ) of powder was determined using fixed funnel method and calculated using the equation tan θ = h/r, Where h and r are the height of the pile and the radius of the pile base, according to the method reported by kannan *et al.,*[10] bulk density, tapped density and compressibility index were determined according to the method described by kannan *et al.,*[10]and calculated by using following equations,

bulk density (D)= weight of the powder/ volume;
Tapped density = weight of the powder/tapped volume;

Compressibility index determined by the carr's index, using the formula

carr's index = [(tapped density-bulk density×100)/ tapped density].

Evaluation of tablets

The formulated Rosigilitazone maleate floating tablets were evaluated for weight variation, hardness, thickness, friability and drug content. The hardness of each formulated batch tablets was checked by using the Monsanto hardness tester (Dr.Schiuniger pharm storn, Switzerland). Roche friabilator (Campbell Electronics, Mumbai, India) and vernier calliper (Mitutoyo corporation, Japan) were used to measure the friability and thickness of the tablets. The weight variation test was carried out according to the official method [11].

Buoyancy/floating test

Buancy studies were conducted using USP type II dissolution apparatus, with 900 ml of 0.1N Hcl (pH 1.2) at 37±0.5ºC temperature and the paddles were rotating at a speed of 75rpm.The randomly selected tablets from each formulation were performed to measure the *floating lag time* or FLT (The time (minutes) taken by the tablet to reach from the bottom of the medium to top of the medium in flask) and *total floating time* or *duration of floating* or TFT (The time for tablet constantly floated on the surface of the medium) [12].

Swelling index studies

The swelling index of the tablets was studied by placing them in 900ml of 0.1N HCl (pH 1.2), the medium was maintained at 37±0.5ºC temperature and paddles rotation speed was 50rpm. The predefined time intervals, tablets were withdrawn, blotted to remove excess surface water and weighed. Swelling is the essential factor to ensure floating and drug dissolution[12]. The swelling index (SI), expressed as a percentage, and calculated using equations, swelling index = Wet weight - Dry weight/ Wet weight*100[13, 14].

In-vitro drug dissolution studies

In vitro release rate of Rosigilitazone maleate from prepared floating tables was studied using USP type I dissolution test apparatus (electro lab TDT-08L). The formulated tablets were placed in a basket containing 900ml of 0.1N Hcl (pH 1.2) dissolution medium and maintained at 37±0.5ºC temperature and rotated at 100rpm. Sink conditions prevail for the whole experiment. Five milliliters of sample were withdrawn at predetermined time intervals, passed through a 0.45µ membrane filter (Nunc, New Delhi, India) and after suitable dilution, analyze the concentration of drug present in the each sample by using a UV spectrophotometer (UV1700CE, Shimadzu, Japan) at 228nm. The initial volume of the sample was maintained by adding fresh pre warmed dissolution medium after each withdrawal.

Drug release kinetics studies

The in vitro drug release data was analyzed the mechanism of release kinetics, according to the following plots: zero-order (cumulative amount of drug release vs. time)[15], first-order (log cumulative percentage of drug remaining vs. time)[16], Higuchi model (cumulative percentage of release vs. square root of time)[17] and Korsmeyer-Peppas model (log cumulative percentage of drug released vs. log time)[18].

Table I. The Composition of Rosigilitazone maleate floating tablets.

S.no	INGREDIENTS	Quantity used in mg						
		F1	F2	F3	F4	F5	F6	F7
1	Drug	10	10	10	10	10	10	10
2	HPMC K4M	40	65.9	51.54	60	50	50	50
3	Xanthan gum	5	5	5	5	3	8	5
4	$NaHCO_3$	21.5	21.5	22.5	22.5	22.3	15.2	30
5	Crospovidone CL-M	29.6	16.8	16.8	16.8	16.8	17.8	16.6
6	Avicel pH 102	51.9	38.8	52.16	43.7	55.9	57	46.4
7	Magnesium Stearate	2	2	2	2	2	2	2

Table II. Results of powder blend precompression parameters

Formulation	Angle of repose (θ)	Tapped Density (g/ml)	Bulk Density (g/ml)	Compressibility Index (%)
F1	23.59 (0.09)	0.521 (0.05)	0.451 (0.04)	12.42 (0.06)
F2	21.44 (0.05)	0.504 (0.02)	0.467 (0.02)	14.51 (0.01)
F3	26.53 (0.15)	0.519 (0.04)	0.422 (0.07)	15.13 (0.04)
F4	20.30 (0.11)	0.569 (0.07)	0.491 (0.03)	10.91 (0.02)
F5	26.19 (0.02)	0.482 (0.03)	0.413 (0.05)	12.14 (0.07)
F6	21.19 (0.04)	0.596 (0.01)	0.417 (0.02)	11.27 (0.04)
F7	22.76 (0.12)	0.545 (0.02)	0.426 (0.04)	12.19 (0.02)

Figures in the parentheses represent ±SD, n=3

Table III. Results of weight, hardness, thickness, friability, drug content, floating lag time and total floating time of Rosigilitazone

Evaluation of tablets	Different formulations						
	F 1	F2	F3	F4	F5	F6	F7
Weight mg± SD (n=20)	160 (2.10)	158(2.29)	160 (4.02)	159 (1.30)	158 (2.40)	162 (3.52)	160 (3.52)
Hardness kg/cm2 ± SD(n=3)	6.0 (0.19)	5.6 (0.34)	5.9 (0.10)	6.2 (0.40)	5.4 (0.31)	5.8 (0.15)	5.9 (0.24)
Thickness mm ± SD (n=5)	3.77(0.09)	3.91 (0.04)	3.97 (0.01)	3.82 (0.04)	3.88 (0.03)	3.98 (0.05)	3.84 (0.04)
Friability %	0.48	0.62	0.57	0.60	0.43	0.68	0.51
Drug content % ± SD (n=3)	24.19 (0.02)	24.19 (0.02)	0.483 (0.02)	0.525 (0.04)	20.19 (0.01)	24.19 (0.02)	0.483 (0.02)
Floating lag time Sec	60	38	26	40	35	48	45
Total floating time hrs	13	18	18	24	24	24	24

RESULTS AND DISCUSSION

Powder blend was evaluated for precompression parameters including angle of repose, bulk density, tapped density and compressibility index. The bulk density and tapped density of the powder blend was in the range from 0.413±0.05 to 0.491±0.03g/ml and 0.482±0.03 to 0.596±0.01g/ml. The angle of repose results of all seven formulations indicates that the powder flow properties range between 20 to 30 degrees, so the type of flow was good and it is supported by the lower compressibility[19]. The results of Carr's index range of 10.91±0.02 to 15.13±0.04% respectively indicating good compressibility and the results of the all formulations flow properties were depicted in **Table II**. The Rosigilitazone maleate floating tablets were formulated using direct compression method and the physical parameters of weight variation, hardness, thickness, friability and drug content of all fabricated tablets were within pharmacopoeial limits and acceptable pharmacotechnical properties. Physical parameters of the designed tablets were given in **Table III**.

Buoyancy and floating studies results of floating lag time (FLT) was found in the range of 26 Sec to 60 Sec and the minimum and maximum total floating time (TFT) among the seven formulations were found to be 13 hrs to 24 hrs respectively. The formulated floating tablet FLT depends on the concentration of gas generating agent (sodium bicarbonate) involved in carbon dioxideformation. Sodium bicarbonate was provided the desired floating ability and the floating lag time increases with decreasing the density of the tablet below one. Penetration of water is slow in F6 formulated tablets, because the presence of higher amount of xanthan gum causing delayed gel formation and subsequently increased the floating lag time. The high concentration of HPMC K4M used formulations provided 24 hrs total floating time. The swelling index of all the formulations were evaluated and formulation (F6) containing high concentration of xanthan gum exhibited higher swelling indices and faster rate of swelling as compared to other formulations. **Table III** shows the floating lag time and total floating time results of all formulated batch tablets.

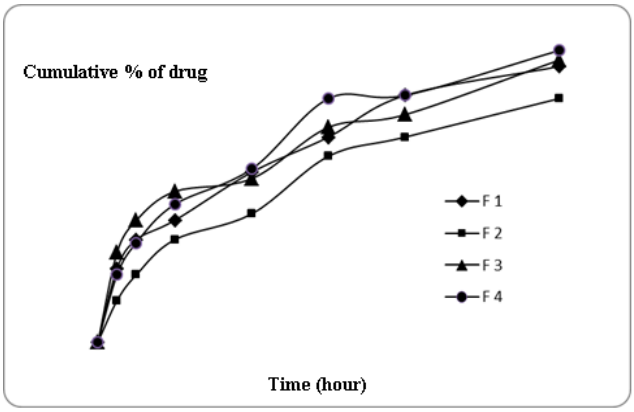

FIGURE 1- In vitro release profiles of Rosigilitazone maleate from batches F1 to F4 floating tablets. The cumulative % drug release from these formulations represents mean ± SD, n=3.

Rosigilitazone maleate was used as model drug to formulate the floating tablets. The different polymers and excipients were used alone or and combinations in the formulations. Incorporation of higher concentration of HPMC K4M in formulation (F2) was found to give slow drug release. The combination of xanthan gum and sodium bicarbonate higher percentage in the formulations (F4, F6, and F7) gives drug release for a longer time. F**igure 1 and 2** indicates the release pattern of all formulations. The Xanthan gum based formulation (F6) exhibit higher rate and extent of drug release. The different formulated batches F4, F6 and F7 provids good drug release of 91%, 92% and 100% respectively.

The dissolution data from 1 to 12hrs drug release kinetics were analyzed according to different kinetic equations, Zero-order, First-order, Higuchi and Korsemeyer-Peppas models. The interpretation of data was done by the regression coefficient method. The regression coefficient value (R^2) and n values of all batches were depicted in **Table IV**. The obtained release kinetics data were plotted according to a first-order equation, the results showed a fair linearity from the formulations F4, F5, F6 and F7. The release profile of the formulations F4, F5, F6 and F7 best fit with higher correlation (R2 > 0.98) was found with Higuchi's model. Whereas remaining all the formulations were followed Korsemeyer-Peppas model. The release exponent 'n' was less than 0.5, indicates the drug release mechanism is diffusion controlled. The finding was according to the previously reported works [20, 21].

CONCLUSION

In this study, Rosigilitazone maleate floating tablets for oral administration was successfully developed by direct compression method, using varying proportions of HPMC K4M, Sodium bicarbonate, Xanthan gum, Crospovidone CL-M, Microcrystalline cellulose and other standard excipients. The precompression properties of blend like angle of repose, bulk density, tapped density, compressibility index and the physical parameters of fabricated floating tablets like weight variation, hardness, thickness, friability, drug content were evaluated and these results shows within the prescribed limit and indicates good flow property. Sodium bicarbonate provided the slow floating lag time and prolonged floating duration. The formulation F6 using higher concentrations of xanthan gum facilitates a higher swelling index. Formulations F4, F5, F6 and F7 shows controlled drug release of 91%, 92% and 100% respectively. Formulations F4, F5 and F7 were followed Higuchi's model, whereas remaining all formulations showed Korsmeyer –peppas model kinetics. The release kinetics of Rosigilitazone maleate exhibited diffusion dominated mechanism. The objective of Rosigilitazone maleate floating tablets steady state plasma concentration was maintained by using optimized techniques has been achieved.

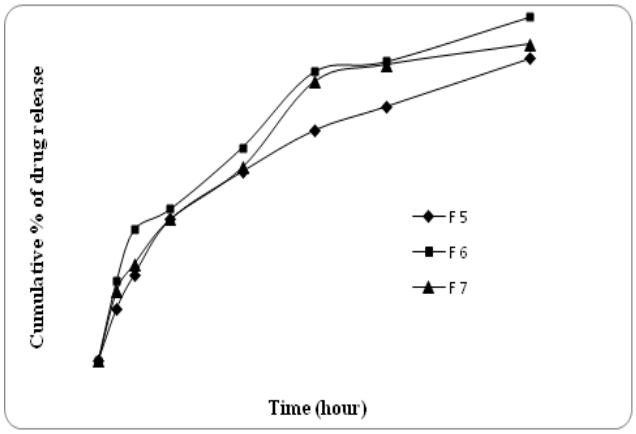

FIGURE 2- In vitro release profiles of Rosigilitazone maleate from batches F5, F6 and F7 floating tablets. The cumulative % drug release from these formulations represents mean ± SD, n=3.

Table IV: Release kinetics data of Rosigilitazone maleate from different formulations

	Formulations						
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
Zero order							
r^2	0.865	0.8157	0.9536	0.9019	0.8869	0.7126	0.8903
First order							
r^2	0.447	0.478	0.8978	0.9108	0.8375	0.7753	0.8110
Higuchi							
r^2	0.9644	0.9515	0.9782	0.9802	0.9927	0.9680	0.9458
Korsmeyer-peppas							
r^2	0.8810	0.9750	0.9801	0.9468	0.9654	0.9501	0.9227
N	0.296	0.389	0.432	0.362	0.361	0.312	0.367

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