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Research Article

DEVELOPMENT AND EVALUATION OF ROSIGLITAZONE MALEATE FLOATING TABLETS

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ABSTRACT

The aim of present study was to develop gatroretentive drug delivery system of Rosiglitazone maleate. Floating tablets of Rosiglitazone maleate was developed using gas forming agents, like sodium bicarbonate, tartaric acid and polymers like HPMC K15M and Xanthan gum. The prepared tablets evaluated in terms of their precompression parameters, physical characteristics, *in vitro* release, buoyancy and buoyancy lag time. The formulation optimized for different concentration of polymers like HPMC K15M and Xanthan gum. The results of *in vitro* release studies showed that formulation (F6) could sustain drug release (98%) for 12h and remain buoyant for 12h. The optimized formulation (F6) was subjected to various kinetic release investigations and it was found that the mechanism of drug release was predominantly diffusion with a minor contribution from polymeric relaxation. Optimized formulation (F6) showed no significant change in physical appearance, drug content, buoyancy lag time or *in vitro* dissolution study after storage at 45 °C/75% RH for three months.

Key words: Rosiglitazone maleate; Floating drug delivery system; HPMC K15M; Xanthan gum; Buoyancy.

INTRODUCTION

The real issue in the development of oral controlled release dosage forms is not just to prolong the delivery of drugs for more than 12 hours, but to prolong the presence of the dosage forms in the stomach or upper gastrointestinal (GI) tract until all the drug is released for the desire period of time[1]. Rapid GI transit could result in incomplete drug release from the drug delivery device in the absorption zone leading to diminished efficacy of the administered dose[2].

Several approaches are currently used to retain the dosage form in the stomach. These include bio adhesive systems,[3] swelling and expanding systems,[4-5] floating drug delivery systems(FDDS),[6-7] and other delayed gastric emptying devices.[8] FDDS, also called hydrodynamically balanced system, is an effective technology to prolong the gastric residence time in order to improve the bioavailability of the drug. [9] This technology is suitable for drugs with an absorption window in the stomach or in the upper part of the small intestine, [10] drugs acting locally in the stomach,[11] and for drugs that are poorly soluble or unstable in the intestinal fluid.[12] FDDS have a bulk density lower than the gastric fluid and thus 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. Based on the mechanism of buoyancy, two distinctly different technologies, i.e. noneffervescent and effervescent systems, have been utilized in the development of FDDS. The effervescent system utilizes matrices prepared with swellable polymers and effervescent components, e.g. sodium bicarbonate and citric acid or stearic acid. The matrices are fabricated such that in the stomach carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the gellified hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy. In noneffervescent FDDS, the drug is mixed with a gel-forming hydrocolloid, which swells on contact with the gastric fluid after oral administration and maintains relative integrity of shape and a bulk density of less than unity within an outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. [13-14]

Rosiglitazone maleate has a half life of (3-4hr) and it reaches a peak plasma concentration after 1hrs and which is absorbed from gastrointestinal tract but solubility decreases with increasing pH in the physiologic rang.[15- 17] which makes Rosiglitazone maleate as suitable candidate for gatroretentive drug delivery system. The purpose of this work was to develop novel sustained release Rosiglitazone maleate floating tablets to increase gastric residence time of Rosiglitazone maleate.

MATERIALS AND METHODS

Materials

Rosiglitazone maleate was obtained as a gift sample from Micro labs Bangalore. Polymers like HPMC K15M and Xanthan gum were obtained as gift samples from Karnataka antibiotics and pharmaceuticals limited Bangalore. All other chemicals used in the study were of analytical grade.

Methods

The composition of different formulations of Rosiglitazone maleate floating tablets is shown in TABLE 1. The ingredients were weighed accurately and mixed thoroughly. Granulation was done with a solution of PVP K-30 in sufficient isopropyl alcohol. The granules (40 mesh) were dried in conventional hot air oven at 45°C. Drying of the granules was stopped when the sample taken from the oven reached a loss on drying (LOD) value of 1 to 3%, as measured by a moisture balance at 105°C. The dried granules were sized through 40/60 mesh, lubricated with magnesium stearate (2%w/w) and purified talc (1%w/w) and then compressed.

Drug polymer compatibility studies

The pure drug and physical mixture of drug and polymers were subjected to IR spectroscopic study using FT-IR spectrophotometer (IRAffinity-1, Shimadzu). The spectra were scanned over the wave number range from 4000 – 400 cm-1.

Dose calculation[18]

For sustained drug release up to 12h, the total dose of drug required was calculated based on the fact that the conventional dose was calculated using the following equation.

D_t= Dose (1+0.693×t/$t_{½}$)

D_t =Total dose, Dose=Immediate release dose, t=Total time period for which sustained release is required, $t_{½}$ = Half life of drug. For Rosiglitazone maleate: D_t= Dose (1+0.693×12/3.5), D_t =6.752mg Rosiglitazone and 8.943mg of Rosiglitazone maleate is equivalent to 6.752mg Rosiglitazone

Evaluation of Rosiglitazone maleate granules

Precompression parameters of Rosiglitazone maleate granules

The flow properties of granules (before compression) were characterized in terms of angle of repose[8], tapped density, bulk density[19], Carr's index[20] .

Physical evaluation of Rosiglitazone maleate floating tablets

Two tablets from each formulation were randomly selected and organoleptic properties such as colour, odour, taste, and shape were evaluated. Thickness and diameter of ten tablets were measured using Vernier calipers. The prepared floating tablets were evaluated for uniformity of weight using 20 tablets[21], hardness (Monsanto tester) [22], friability using 10 tablets (Roche Type friabilatror).[23]

Drug content estimation

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was added in 100ml of 0.1M hydrochloric acid, followed by stirring. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 318nm using 0.1 M hydrochloric acid as blank.

***In vitro* Buoyancy Studies**

The *in vitro* buoyancy was determined by the floating lag time. The tablets were placed in 100-mL beaker containing 0.1M 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**

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 (10 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with 0.1N hydrochloric acid. Absorbance of these solutions was measured at 318 nm using a UV/Visible spectrophotometer. The percentage drug release was plotted against time to determine the release profile.

***In vitro* drug release kinetic studies**

Kinetic model had described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. In order to study the exact mechanism of drug release from the tablets, drug release data was analyzed according to zero order[24], first orde[25], Higuchi square root[26], Korsmeyer- Peppas model[27].The criteria for selecting the most appropriate model was chosen on the basis of goodness of fit test. The data were processed for regression analysis using graph pad prism.

RESULTS AND DISCUSSION

Compatibility studies of Rosiglitazone maleate

The major IR peaks observed in Rosiglitazone maleate were C=C (1616.3 CM^{-1}), C-O (1062.7 CM^{-1}), NH (3430.51 CM^{-1}). IR peaks observed in physical mixture of Rosiglitazone maleate and HPMC K15M were C=C (1618.3 CM^{-1}), C-O (1051. 7 CM^{-1}), NH (3430.5CM^{-1}). IR peaks observed in physical mixture of Rosiglitazone maleate and Xanthan gum were C=C (1641.3 CM^{-1}), C-O (1051.32CM^{-1}), NH (3430.5CM^{-1}) as shown in FIG1. There were no extra peaks were observed. Thus the chosen polymers were compatible with Rosiglitazone maleate.

Table 1: Composition of different floating tablet formulation of Rosiglitazone maleate

Ingredients	F1	F2	F3	F4	F5	F6
Rosiglitazone maleate	9	9	9	9	9	9
HPMC K15M	45	54	63	-	-	-
Xanthan gum	-	-	-	45	54	63
Sodium bicarbonate	20	20	20	20	20	20
Tartaric acid	10	10	10	10	10	10
PVP-K-30	4.5	4.5	4.5	4.5	4.5	4.5
Dicalcium phosphate	57	48	39	57	48	39
Magnesium Stearate	3	3	3	3	3	3
Talc	1.5	1.5	1.5	1.5	1.5	1.5

Table 2: Results of precompression flow properties of granules of Rosiglitazone maleate

Formulation code	Evaluation parameters			
	Bulk density (g/cc) ± SD	Tapped density (g/cc) ± SD	Angle of repose (θ) ± SD	Carr's index ± SD
F1	0.486 ± 0.011	0.564 ± 0.041	20.1^0 ± 0.7	13.82 ± 0.74
F2	0.483 ± 0.005	0.578 ± 0.096	21.7^0 ± 1.0	15.91 ± 0.52
F3	0.468 ± 0.113	0.568 ± 0.013	23.7^0 ± 0.4	17.60 ± 0.79
F4	0.442 ± 0.035	0.521 ± 0.038	21.5^0 ± 0.8	15.16 ± 0.32
F5	0.443 ± 0.147	0.531 ± 0.052	22.3^0 ± 0.3	16.57 ± 0.27
F6	0.453 ± 0.012	0.547 ± 0.016	23.2^0 ± 1.2	17.18 ± 0.13

SD = Standard deviation (n=3)

Table 3: Results of post compression properties of Rosiglitazone maleate floating tablets

Formulation code	Evaluation parameters			
	Thickness ± SD (mm)	Hardness ± SD (kg/cm^2)	Friability (%) ± SD	Average weight variation ± SD
F1	2.80 ± 0.021	3.9 ± 0.1	0.359 ± 0.05	0.149 ± 0.577
F2	2.82 ± 0.034	4.2 ± 0.1	0.678 ± 0.02	0.149 ± 1.527
F3	2.80 ± 0.012	4.1 ± 0.1	0.420 ± 0.08	0.148 ± 0.577
F4	2.81 ± 0.001	4.2 ± 0.1	0.399 ± 0.03	0.151 ± 0.010
F5	2.83 ± 0.005	4.2 ± 0.1	0.566 ± 0.01	0.152 ± 0.011
F6	2.80 ± 0.011	4.3 ± 0.1	0.481 ± 0.06	0.149 ± 0.001

SD = Standard deviation (n=3)

Precompression parameters of Rosiglitazone maleate granules

The formulations showed good flow property and compressibility index TABLE 2. Angle of repose ranged from 20.01± 0.7 to 23.7± 0.4 and the compressibility index ranged from 13.82± 0.74 to 17.60 ±0.79. The LBD and TBD of the prepared granules ranged from 0.442 ± 0.035 to 0.486 ± 0.011 and 0.521 ± 0.038 to 0.578 ± 0.096 respectively. The results of angle of repose indicates good flow property of the granules and the value of compressibility index further showed support for the flow property.

Post compression parameters of Rosiglitazone maleate floating tablets

The shape of the tablets of all formulations remained off white, smooth, flat faced circular with no visible cracks. The thickness and diameter of tablets was measured by Vernier calipers and ranged between 2.80 ± 0.021 to 2.83 ± 0.005 mm, 10.80 to 11.02 mm respectively. The hardness of the tablets was measured by Pfizer tester (Biological museum, Mumbai, India) and was in between 3.9 ± 0.1 to 4.3 ± 0.1 kg/cm2. The friability was measured by Friabilatror (Thermionic, Campbell Electronics, Mumbai) and was found to be 0.359 ± 0.05 to 0.678 ± 0.02%, which is an indication of satisfactory mechanical resistance of the tablets. The drug content estimations showed values in the range of 95.7 ± 0.005 to 97.16 ± 0.008% as shown in Table3 which reflects good uniformity in drug content among different formulations. All the tablets passed weight variation test as the % weight variation was within the Pharmacopoeial limits of ±7.5% of the weight. The results are shown in TABLE 3. All the formulations showed values within the prescribed limits for tests like hardness, friability and weight variation which indicate that the prepared tablets are of standard quality.

***In vitro* buoyancy studies**

All the tablets were prepared by effervescent approach. Sodium bicarbonate was added as a gas-generating agent. Sodium bicarbonate induced carbon dioxide generation in presence of dissolution medium (0.1 M hydrochloric acid). The combination of sodium bicarbonate and Tartaric acid provided desired floating ability and therefore this combination was selected for the formulation of the floating tablets. It was observed that the gas generated is trapped and protected within the gel, formed by hydration of polymer (HPMC), thus decreasing the density of the tablet below 1 and tablet becomes buoyant. The tablet swelled radially and axially during *in vitro* buoyancy studies. In this study, penetration of water into tablets prepared with Xanthan gum was rather slow, causing delayed gel formation and subsequent increase in the floating lag time compared to the tablets prepared with HPMC K15M TABLE 4.

***In vitro* release studies**

In vitro dissolution studies of all the formulations of floating tablets of Rosiglitazone maleate were carried out in 0.1N HCL. The study was performed for 12h and cumulative drug release was calculated at every one hour time interval. *In vitro* dissolution studies of all the formulations are shown in Fig 2. Two different polymers like HPMC K15M and Xanthan gum TABLE 1 were used to prepare floating tablets. It was observed that the type of polymer influences the drug release pattern. All the formulations contained equal amount of gas generating agent (sodium bi carbonate) and Tartaric acid. A significantly higher rate and extent of drug release was observed from the batches based on HPMC K15M.Varying the amount of HPMC K15M affect the drug release.

Table 4: Results of drug content of Rosiglitazone maleate floating tablets

Tablet formulation	Calculated value (mg)	Estimated value (mg)±SD	%Drug content ±SD
F1	9	8.677 ± 0.003	95.78 ± 0.007
F2	9	8.602 ± 0.006	95.7 ± 0.005
F3	9	8.422 ± 0.005	95.76 ± 0.006
F4	9	8.702 ± 0.005	96.63 ± 0.001
F5	9	8.678 ± 0.004	96.47 ± 0.006
F6	9	8.744 ± 0.006	97.16 ±0.008

SD = Standard deviation (n= 3)

Table 5: Results of in vitro buoyancy studies of Rosiglitazone maleate floating tablets

Formulation code	Floating lag time (S)	Total floating time (h)
F1	25.33 ±1.52	>12
F2	47.0 ± 1.0	>12
F3	68.6 6 ± 0.57	>12
F4	72.66 ± 2.08	>12
F5	115.0 ± 2.0	>12
F6	147.66 ± 2.08	>12

SD = Standard deviation (n= 3)

Table 6: Kinetic release data of different model for optimized formulation (F6)

Model	Slope	R^2
Zero order	7.183	0.9089
First order	-0.1284	0.8603
Higuchi	29.06	0.9969
Korsmeyer-Peppas	0.5229	0.9881

SD = Standard deviation (n= 3)

Table 7: Stability study (40 °C/75%RH) of Optimized Formulation (F6)

Parameters	1st month	2nd month	3rd month
Physical appearance	Off white flat smooth faced	Off white flat smooth faced	Off white flat smooth faced
Weight variation (mg)	0.149 ± 0.001	0.149 ±0.001	0.149 ±0.001
Hardness (Kg/Cm^2)	4.3 ± 0.1	4.2 ± 0.1	4. 2 ± 0.1
Friability (%)	0.581 ± 0.007	0.521 ± 0.02	0.543 ± 0.121
Drug content (%)	97.02 ± 1.01	96.21 ± 0.92	95.43 ± 0.64
Buoyancy lag time(s)	150.34 ± 1.23	152.12 ± 1.07	153.08 ± 0.32
Total floating time(hrs)	12	12	12
Buoyancy on disturbing	Float	float	float
In vitrto release (%)	97.12 ± 0.54	96.37 ± 0.73	95.26 ± 0.87

SD = Standard deviation (n= 3)

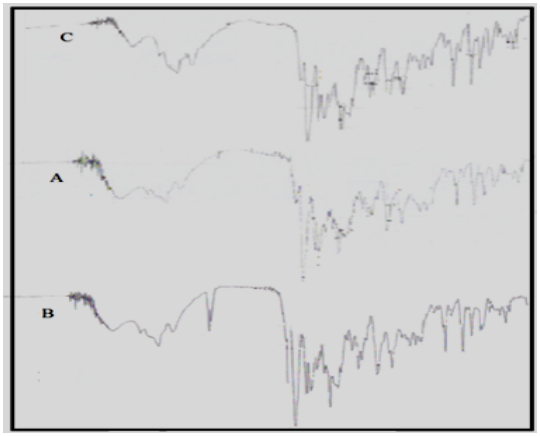

Fig.1: Compatibility studies: A. Rosiglitazone maleate, B. Physical mixture of Rosiglitazone maleate + HPMC K15M, C. Physical mixture of Rosiglitazone maleate + Xanthan gm

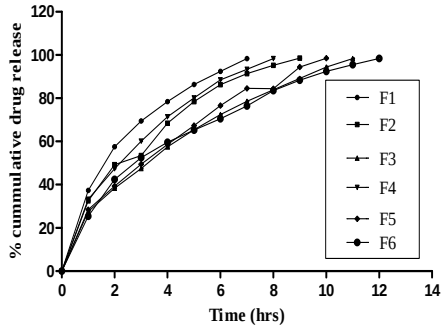

Fig. 2: Comparison of *in vitro* dissolution profiles of F1 to F6

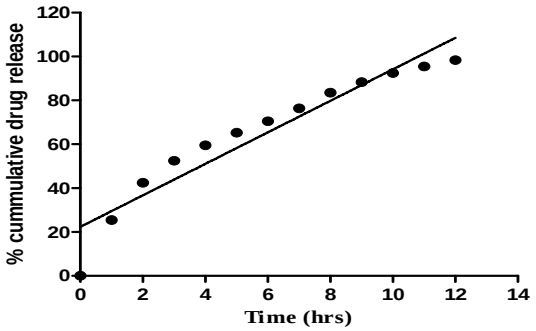

Fig. 3: Zero order release kinetics of optimized formulation (F6)

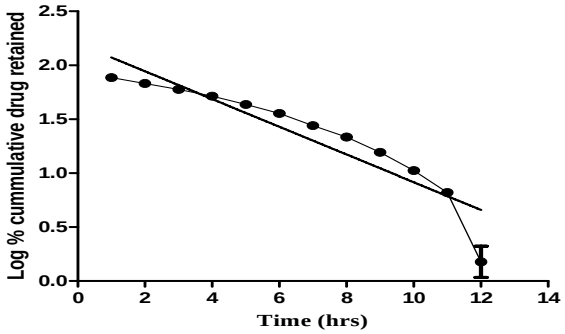

Fig. 4: First order release kinetics of optimized formulation (F6)

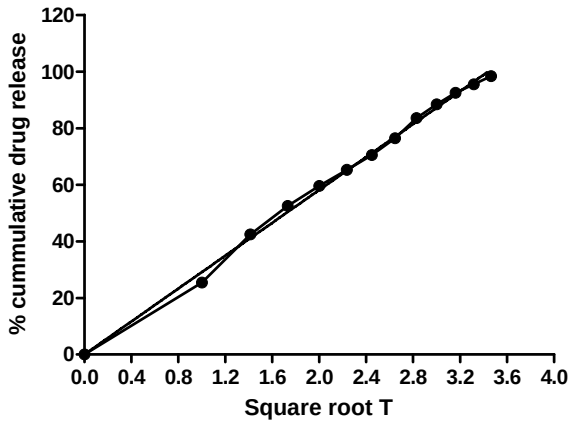

Fig. 5: Higuchi matrix release kinetics of optimized formulation (F6)

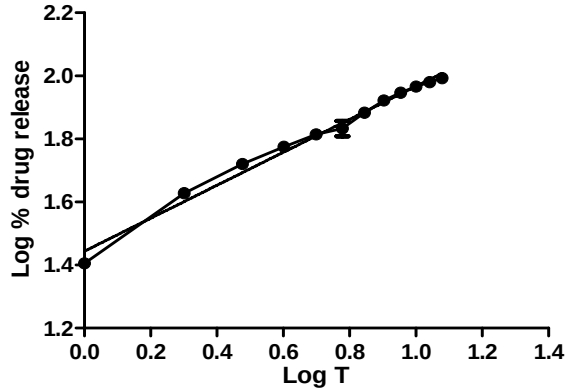

Fig. 6: Korsmeyer and Peppas release kinetics of optimized formulation (F6)

Drug release from Xanthan gum was lesser owing to its high viscosity and also due to less permeability of water to Xanthan gum. More over HPMC K15M containing tablets F1-F3 could not bear their matrix shape until 12 h and the released the drug before 12 h. Tablets F4-F6 containing Xanthan gum in the increasing concentration F6 was found to sustain drug release up to 12 hrs.

Analysis of release mechanism

The drug release data of optimized formulation (F6) were fitted to models representing Higuchi's, zero order, first order and Korsmeyer's equation kinetics to know the release mechanisms. The data were processed for regression analysis using Graph pad prism statistical function. The results are shown in Table6 and graphs in figure 3 to 6 In the present study, in vitro release profiles could be best expressed by Higuchi's equation as optimized formulation (F6) showed good linearity (R2: 0.9969) indicates that diffusion is dominant mechanism of drug release with these formulations. The values of slope for the korsemeyer - Peppas model indicates that drug release from the tablets were non fickian diffusion.

Stability study of optimized formulation (F6)

The optimized floating tablets (F6) were selected for stability study on the basis of *in vitro* buoyancy and *in vitro* drug dissolution studies. The tablets were investigated at 40°C/75% RH for 3 months. From the data, the formulation is found to be stable under the conditions mentioned before since there was no significant change in the percentage amount of drug content TABLE 6. Thus, it was found that the floating tablets of Rosiglitazone maleate (F6) were stable under these storage conditions for at least 3 months.

CONCLUSION

This study discusses the preparation of floating tablets of Rosiglitazone maleate. The effervescent-based floating drug delivery was a promising approach to achieve *in vitro* buoyancy. The addition of gel-forming polymer HPMC K15 M, Xanthan gum and gas-generating agent sodium bicarbonate was essential to achieve *in vitro* buoyancy. Addition of Tartaric acid, to achieve buoyancy under the elevated pH of the stomach, caused an enhancement in drug release. The type of polymer affects the drug release rate and the mechanism. The *in vitro* drug release profiles obtained for formulation (F6) containing Xanthan gum showed controlled drug release for 12hrs, emerging as best formulation. Mechanism of drug release of optimized formulation (F6) found to be Zero order non fickian diffusion. Good stability was observed for 3 months during stability studies.

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