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Formulation and *In-Vitro* Evaluation of Gastro Retentive Rosiglitazone Maleate Floating Tablet

Dhankhar Neelam[1]*, Kumar Sunil[2], Goyal Surinder[3], Ramana Jaspreet[4], Mishra Sushmita[2]

[1]Department of Pharmaceutical Sciences, Ch. Devi Lal College of Pharmacy, Jagadhari, Yamuna Nagar, Haryana, India.
[2]Department of Pharmaceutical Sciences, Dr. K N Modi Institute of Pharmaceutical Education and Research, Modi Nagar, Dist. Ghaziabad, Uttar Pradesh, India.
[3]Vidyasagar Institute of Polytechnic & Pharmacy college, Dist. Ahlupur, Punjab, India.
[4]Department of Pharmaceutical Sciences, Chandigarh College of pharmacy, Mohali, Punjab, India.

ABSTRACT

Rosiglitazone is an antidiabetic agent used in management of type-two diabetes mellitus. Rosiglitazone maleate 160 mg is being formulated as an approach to increase gastric residence time and thereby improve its bioavailability using by direct compression technique. The varying proportion of rate controlling polymer HPMC K4M, Swelling agent (Crospovidone CL-M), Gas forming agent (sodium bicarbonate) were used in these formulations. The different formulations of compressed floating tablets were evaluated such as physical appearance, thickness, diameter, hardness, weight variation, and dissolution. All the Formulated tablets gave satisfactory results. A lesser floating lag time (FLT) and a prolonged floating duration could be achieved by varying the concentration of rate controlling polymer and gas forming agent. Drug release for F1, F2 and F3 were found to obey Peppas-Korsmeyer's release kinetics, F4 and F5 were found to obey Higuchi's release kinetics. All the formulations were buoyant, in these formulations F1, F3 were buoyant for 18 hours. Formulations F2, F4 were buoyant up to 24 hours. Remaining formulation F5 was found to buoyant until the drug soluble as well as gave better-controlled drug release in comparison to other formulations. Formulated floating tablets best fitted to Higuchi's release kinetics and zero order kinetics.

KEY WORDS: Gastro retentive, Floating tablet, Rosiglitazone, HPMC K4M, Direct compression Technique.

*** Corresponding Author:**
Neelam Dhankhar
Ch. Devi Lal Collage of Pharmacy
Dist. Yamuna Nagar, Haryana, India 135003
Phone No.: +91-9568972778
E-mail – reenadhankhar@gmail.com

INTRODUCTION

Gastro retentive system can remain in the gastric region for several hour 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 high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestine. A gastro retentive dosage form will release the drug over an extended period in the stomach and upper gastrointestinal tract (GIT). Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesive[1,2], flotation[3], sedimentation[4,5], expansion,[6,7] modified shape system[8,9] or by the simultaneous administration of pharmacological agents[10] that delay gastric emptying. Floating drug delivery system is also referred as Hydrodynamically Balanced System (HBS) or Gastro Retentive Drug Delivery System (GRDDS).

The excellent floating system is effective only in the presence of sufficient fluid in the stomach; otherwise, buoyancy of tablet may be hindered. This limitation can be overcome by using a combination of floating system with other gastro retentive approaches[11]. Gastro retentive drug delivery system are formulated as floating micropaticles, tablets pellets, capsules etc. among which the multiparticulate system are more effective than the single unit dosage forms.[12,13]

As per mechanism of expansion of expandable dosage form, the generation of gas on contact with gastric juice is preferred. While various gases will be suitable from the physiological point of view, among of them, nitrogen, nitrous oxide, methane and other gases, expansion with CO_2 is particularly preferred since this can be released readily and in a relatively large amount. In principle suitable substance from which CO_2 can be released are various carbonates and hydrogen carbonates. On account of good tolerability and high yield, Hydrogen Carbonate or Sodium Hydrogen Carbonate ($NaHCO_3$) is preferred[14].

Due to release of gases they get entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme.

MATERIALS AND METHODS

HPMC (Dow chemical's, USA of Grade K4MCR), Xanthan Gum (KR & CO international ltd. of grade USNF), Sodium bi carbonate (Dr.Paul lohnmann,gremany), Cross povidone (BASFchemicals, switzerland of grade CL-M), Avicel (Signet chemicals ,Mumbai of grade pH 101), Magnesium stearate (St.louis, Missouri). All the chemicals were purchased.

PREPARATION OF TABLETS

Rosiglitazone tablets were formulated by direct compression technique using hydrophilic polymer (HPMC K4M), gas generating agent and swelling agents in each formulation. The composition of different excipients in formulation are listed in table 1. Drug and polymer were sifted through sieve no. 36 and weighed accurately. Then both the drug and polymers were blended for 15 minutes. Magnesium stearate was sifted through sieve no. 44 and mixed in the above blend and blended upto 5 minutes. Blend was compressed using round shape punches on cadmach 16-station rotary compression machine.

Table 1: Final formulation batches

S. No.	Ingredients	F1	F2	F3	F4	F5
1	Drug	10.64	10.64	10.64	10.64	10.64
2	HPMC K4mcr	40	60	65.9	60	50
3	Xanthan Gum	5	5	5	5	3
4	Sodium bi Carbonate	22.5	22.5	22.5	22.5	22.5
5	Crospovidone CL-M	29.8	16.8	16.8	16.8	16.8
6	Avicel 102	51.9	38.9	-	43.0	55.0
7	Mg stearate	2.0	2.0	2.0	2.0	2.0
8	Avg. wt.	160	160	160	160	160

EVALUATION OF TABLET

General Appearance

The general appearance of tablets, its visual identity and overall 'elegance' is essential for consumer acceptance for monitoring the production process.

Size and Shape

The shape and dimensions of compressed tablets were determined by the type of tooling during the compression process.

Thickness and Diameter

Ten tablets were measured using vernier caliper. Ten tablets from each formulation were used and average value was calculated and given in table 2.

Hardness

From each batch, five tablets were tested using Monsanto Hardness Tester and hardness is given in Table 2.

Friability

The friability test was performed for all the formulated tablets using Roche Friabilator. Ten tablets were taken and their weight was determined (W_0) then they were placed in a rotating drum. Then they were subjected to 100 revolutions. After completion of 100 revolutions or 4 min of time at 25 rpm, the tablets were again weighed (W). The percentage friability (f) was calculated by the formula given and as are given in Table 2.

$$\mathbf{f = W_0 - W / W_0 \times 100}$$

Acceptance criteria: The friability value should be less than 1.0%

Swelling Index Test:

The swelling index of the tablets was determined in the 0.1 N HCL (pH 1.2),100 rpm at 37^{o}C .the swollen weight of the tablets was determined at predefined time intervals (1hr,2hr,3hr,4hr) and swelling index was calculated by the following equation (Table 3)

$$\mathbf{Swelling\ index = W_t - Wo / Wo}$$

Where, **Wo** is the initial weight of the tablet, and $\mathbf{W_t}$ is the weight of the tablet at time ***t***.

Buoyancy / Floating Test:

The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remained buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time

(BLT) and total duration of floatation i.e. as long the dosage form remains buoyant is called Total Floating Time (TFT).

***In-Vitro* Dissolution Studies:**

The different concentration of HPMC K4M polymer was used to prepare the floating matrix tablets. Generally these polymers were increased swelling index and it's also able to maintain the integrity of the tablets. The higher concentration of rate controlling HPMC K4M polymer decreased the drug release. Gas generating agent containing sodium bicarbonate used for all formulations. The CO_2 generated by effervescent gets entrapped in the gel layer and helps the tablets become buoyant in less time.[18,19] Release profile of drug of different batches of tablet based on floating drug delievery system is shown in figure 1.

RESULTS AND DISCUSSION

Oranoleptic Properties:

The drug powder was analyzed for taste and odour. It is tasteless and odourless.

Evaluation of Formulation on the basis of following parameters

- ♦ Tablet thickness
- ♦ Tablet hardness
- ♦ Swelling index
- ♦ Total floating time

Hardness

The hardness of all formulas was kept at 5-7 kp and shown in table 2.

Buoyancy / Floating Test

The tablet floating lag time (FLT) was found to be less than 1 minute and total floating time more than 24 h or until the drug soluble in media as shown in table 2.

The floating lag time may be explained as a result of the time required for dissolution medium to penetrate the tablet matrix and develop the swollen layer for entrapment of CO_2 generated in situ. The tablet mass decreased progressively due to Liberation of CO_2 and release of drug from the matrix. On the other hand, as solvent front penetrated the glassy polymer layer, the swelling of HPMC K4M and

Crospovidone CL-M caused an increase in volume of the tablet. The combined effect is a net reduction in density of the tablets. As the density of tablet falls below 1, the tablet becomes buoyant which prolongs the duration of floatation beyond 24 hours[15].

Table 2: Physical evaluation of tablets for final formulation batch

S. No.	Colour	Thickness (mm)	Hardness (kp)	Weight (mg)	FLT (sec)	TFT (Hour)
F1	off white	3.77-3.86	6.0-7.0	160±5	60	3
F2	off white	3.91-4.00	5.6-6.8	158±5	38	18
F3	off white	3.97-4.05	5.9-7.0	160±5	26	18
F4	off white	3.82-3.87	6.2-6.9	159±5	40	24
F5	off white	3.88-3.92	5.4-6.3	158±5	35	24

SWELLING INDEX TEST:

Tablets composed of polymeric matrices form a gel layer around the tablet core when they come in contact with media. This gel layer governs the drug release. The kinetics of swelling is important because the gel barrier is formed by media penetration. Swelling is also vital to ensure floating.

To obtain floating, the balance between swelling and media acceptance must be restored[16,17] the swelling index of formulation F2 was found to be best and this formulation was made by using HPMC K4M at different concentrations. It has a good swelling index and swelling rate as shown in Table 3.

Table 3: Swelling index and diameter test for final formulation batches

S.No.	SWELLING INDEX (mg)			
	1 hr	2hr	3hr	4hr
F1	1.108	1.32	1.679	1.594
	1.142	1.593	1.716	1.621
F2	1.052	1.656	1.925	2.137
	1.112	1.65	2.075	2.175
F3	1.124	1.562	1.656	1.237
	1.003	1.492	1.725	2.137
F4	1.125	1.606	1.88	1.375
	1.156	1.702	1.856	1.237
F5	1.562	1.45	2.018	4.393
	1.331	1.432	1.706	3.837

Study of Release Kinetics:

In vitro dissolution has been recognized as an important release element in drug development under certain conditions it can be used as a surrogate for the assessment of bioequivalence the quantitative interpretation of the values obtain in the dissolution assay is facilitated the usage of a generic equation that mathematically translate the dissolution curve in function of some parameters related with the pharmaceutical dosage form. In some cases, that equation can be deduced by a theoretical analysis and model independent methods can be used.

The various release kinetics in which the experimental data is fitted and drug release rate is predicted as a function of some variable (eg.time). The suitability of equation is judged on the basis of best fit to the equation using statistical like R^2value. Study of release kinetic was carried out by fitting the data into the following models:

- Zero Order Kinetics
- First Order Kinetics
- Higuchi Model
- Peppas-Korsmeyer's Model
- It was found that F1,F2 and F3 obey Peppas-Korsmeyer's release kinetics , F3 was found to obey Korsmeyer's release kinetics, F4, F5 was found to obey Higuchi's release kinetics, All the formulations were buoyant, in this formulation F1, F3 buoyant for 18 hours. Formulations F2, F4 was buoyant up to 24 hours. Remaining formulations F5 were found to buoyant until the drug soluble as well as gave better controlled drug release in comparison to other formulations.
- Formulated floating tablets best fitted to Higuchi's release kinetics and zero order kinetics.[20]

Table 4: Drug release profile of different batches of tablet based on Floating drug delivery system

S. No.	Time (hrs)	F1	F2	F3	F4	F5
1	0.5	23	19	28	21	15
2	1	32	22	38	31	25
3	2	38	32	47	43	41
4	3	44	40	51	54	55
5	6	64	58	67	76	67
6	8	77	65	71	77	74
7	12	86	76	88	91	88

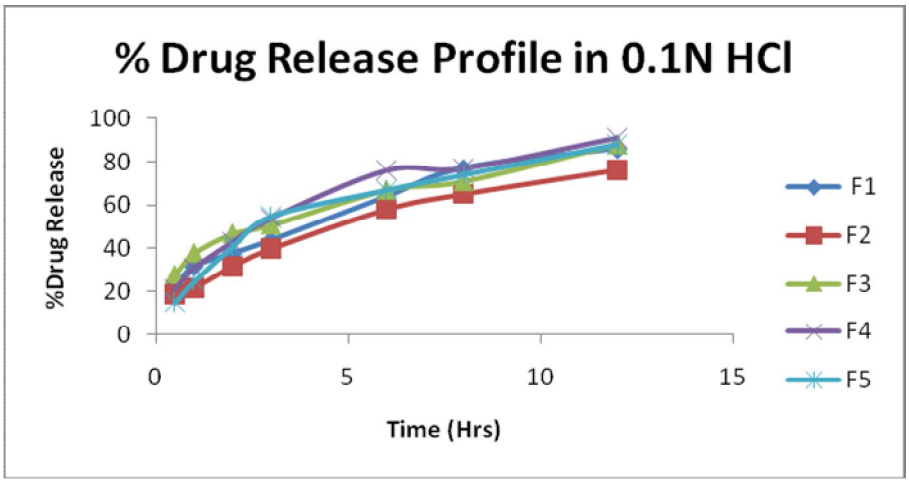

Figure 1: Drug release profile of different batches of tablet based on floating drug delivery system

Table 5: The rate constant and r^2 value of final formulations.

S. No.	ORDER OF KINETICS				
		ZERO ORDER	FIRST ORDER	HIGUCHI MODEL	PEPPAS-KORSMEYER
F1	Rate constant	5.5283	0.2542	10.893	0.0928
	r^2 value	0.9577	0.9124	0.967	0.9763
F2	Rate constant	5.767	0.1133	22.238	0.5067
	r2 value	0.8899	0.9834	0.9958	0.9963
F3	Rate constant	4.7904	0.3422	9.5	0.0708
	r^2 value	0.9536	0.8978	0.9782	0.9801
F4	Rate constant	5.8576	0.3422	11.964	0.0927
	r^2 value	0.9009	0.9108	0.9802	0.9468
F5	Rate constant	5.9135	0.3062	12.25	0.1025
	r^2 value	0.8869	0.9375	0.9927	0.9254

CONCLUSION:

Rosiglitazone is an antidiabetic agent used in management of type-two diabetes mellitus. After 8 to 12 weeks of Rosiglitazone monotherapy, the dose may be doubled in case of insufficient response and this leads to higher incidence of dose dependent side effects. Such as gastro-intestinal disturbances, headache, altered blood lipids, oedema, hypoglycaemia**.** Further, adverse events of clinical significance which are reported frequently with conventional instant release dosage forms of the drug are oedema, anaemia and weight gain **.** Thus, there is a need to maintain Rosiglitazone at its steady state plasma

concentration. Hence, the study was carried out to formulate and evaluate floating dosage form of rosiglitazone maleate as a model drug and final batch formulation parameters having, less floating lag time, and prolong drug release.

Hydrodynamically Balanced Tablet of an antidiabetic drug rosiglitazone maleate 160mg can be formulated as an approach to increase gastric residence time and thereby improve its bioavailability using by direct compression technique. The varying the proportion of rate controlling polymer HPMC K4M, Swelling agent (Crospovidone CL-M),Gas forming agent (sodium bicarbonate) was used in these formulations.

The different formulations of compressed floating tablets were evaluated such as physical appearance, thickness, diameter, hardness, weight variation, content uniformity, assay and dissolution. All the Formulated tablets gave good results. . A lesser floating lag time (FLT) and a prolonged floating duration could be achieved by varying the concentration of rate controlling polymer and gas forming agent.

The *In vitro* dissolution study was performed for different formulations. These formulations were subjected to various model dependent kinetics like Zero order, Higuchi, Korsmeyer release kinetics. The release profile exhibiting maximum r^2 value was found to obey that particular kinetics.

Formulated floating tablets best fitted to Higuchi's release kinetics and zero order kinetics.

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