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ORIGINAL RESEARCH ARTICLE

Formulation and Evaluation of Combined Floating Bilayer Tablet of Metformin, Pioglitazone and Glimepiride

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ABSTRACT

The objective of present investigation was to design the concept of hydro dynamically balanced bilayered tablet containing glimepiride and pioglitazone hydrochloride as immediate release layer and metformin hydrochloride as sustain release floating layer. Floating layer of metformin hydrochloride was prepared by employing different grades of gel forming agent and by various gas generating agent. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, *in vitro* buoyancy, swelling index and dissolution studies. The prepared tablets exhibited satisfactory physico-chemical characteristics. All the prepared batches showed good *in vitro* buoyancy. The tablet swelled radially and axially during *in vitro* buoyancy studies. It was observed that the tablet remained buoyant for 12 hours. The drug release from the tablets was sufficiently sustained.

Key words: Hydro dynamically balanced, Bilayer tablets, Metformin hydrochloride, Glimepiride, Pioglitazone, Floating.

1. INTRODUCTION

The idealized objective of any drug delivery pinpoints two critical aspects of utmost importance i.e. spatial placement and temporal delivery. Drug delivery system is becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biological parameters pertinent to their performances [1]. Among the various systems; gastric floating drug delivery systems (GFDDS) offer numerous advantages. This system is floating on the gastric contents; the drug is released slowly at a desired rate from the stomach [2]. Metformin hydrochloride is an orally administered biguanide derivative widely used in the treatment of non-insulin dependent diabetes mellitus. It improves glycaemic control by enhancing insulin sensitivity in liver and muscle. In humans, metformin hydrochloride is incompletely absorbed and predominantly excreted in urine with a half life of 4-6 hours [3]. Metformin Hydrochloride has a property of a strong base (pKa = 11.5) and is protonated under physiological pH condition. The ionized metformin hydrochloride has a tendency to be absorbed to the negatively charged intestinal epithelium affecting the drug absorption pattern [4].[4] Thus, the absorption window is predominantly in small intestine and follows a saturable dose dependent mechanism [5,6]. A conventional oral sustained release formulation however, releases most of the drug content in a colon, which requires that the drug should have absorption window either in colon or throughout the GIT. Metformin hydrochloride has poor colonic absorption in healthy human subjects [6,7]. Release of metformin hydrochloride after the small intestine is thus, of no therapeutic value. The conventional strategies of prolonging the release of metformin hydrochloride from the dosage forms throughout the GIT would not be effective for metformin hydrochloride formulation as it is primarily absorbed from the small intestine [8]. Thus development of gastro retentive sustained release formulation for metformin hydrochloride would be a better alternative to the conventional sustained release formulations. Glimepiride is one of the generation sulfonylurea drug useful for control of diabetis mellitus, type 2. Preclinical investigation of glimepiride suggest a number of potential benefit over sulfonylurea currently

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available including lower dosage, rapid onset possibly due to less stimulation of insulin secretion and more pronounced extra pancreatic effects. Pioglitazone hydrochloride selectively stimulates the nuclear receptor peroxisome proliferator-activated receptor PPAR-γ and to a lesser extent PPAR-α. It modulates the transcription of the insulin-sensitive genes involved in the control of glucose and lipid metabolism in the muscle, adipose tissue, and the liver. As a result, pioglitazone hydrochloride reduces insulin resistance in the liver and a peripheral tissue increases the expense of insulin-dependent glucose, decreases withdrawal of glucose from the liver, reduces quantity of glucose, insulin and glycated hemoglobin in the bloodstream. With three different mode of action, the combination of glimepiride, pioglitazone hydrochloride and metformin hydrochloride help the body cope with high blood sugar more efficiently. Immediate action of glimepiride and pioglitazone hydrochloride will be helpful to control excess sugar, which will be maintained by metformin hydrochloride action later on. Thus, the developed single tablet will be sufficient instead of two to three tablets of both drugs per day, and it will also increase patient compliance and therapeutic efficacy [9].

Thus, sustained release gastro retentive tablet would be ideally suited to formulate in which metformin hydrochloride as gastro retentive layer (FDDS) in the light of its PK/PD properties as already discussed. With these considerations, the aim of present study was to design the concept of bilayer gastro retentive tablet containing glimeperide and pioglitazone hydrochloride for immediate release using sodium starch glycollate as super disintegrant and floating sustained release layer of metformin hydrochloride using HPMC, Sodium carboxy methyl cellulose as viscosity inhancer, carbopol as gel forming agent and sodium bicarbonate, citric acid a gas-generating agent. Thus, an effervescent floating tablet was developed and evaluated for floating lag time and in vitro drug release and in vivo studies.

2. MATERIALS AND METHODS

2.1 Material

Metformin was obtained as a gift sample from Shreya Life Sciences, Aurangbad. HPMC K100LV, HPMC K15M, HPMC K4M, HPMC K100M, Betacyclodextrin and Carbopal 934, Sodium bicarbonate, citric acid, Microcrystalline cellulose PH 102, Cross povidone, Sodium starch glycolate, PVP K30, Sodium Carboxy methyl cellulose obtained as a gift sample from Danish laboratories, Ujjain. Rests of all the chemicals are of laboratory grade.

2.2 Evaluation of Pre-compression parameters:

The granules of all the formulations were evaluated for angle of repose, bulk density, tapped density, compressibility index, hausner ratio as per the procedure described in I.P. The data's are shown in (Table 1).

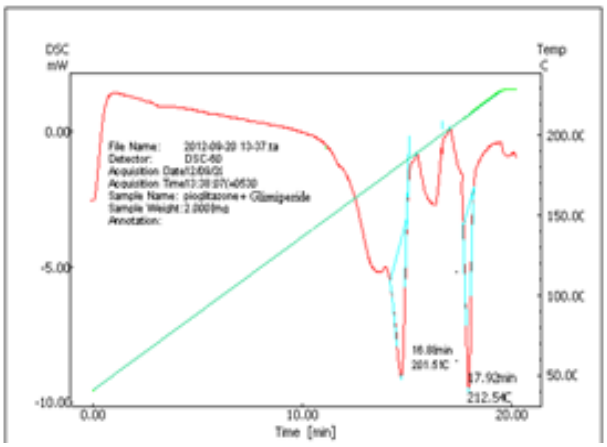
Table 1: Bulk density, tapped density, hausner's ratio, compressibility index, angle of repose, moisture

Formulation	Bulk density	Tapped density	Hausner's ratio	Compressibility index (%)	Angle of repose	Moisture
F-1	0.58	0.67	1.15	13.43	30.10	2.43
F-2	0.66	0.76	1.15	13.15	29.92	2.32
F-3	0.69	0.76	1.10	12.00	27.40	2.47
F-4	0.64	0.75	1.17	14.66	26.98	2.48
F-5	0.59	0.69	1.16	14.49	30.78	2.21
F-6	0.66	0.78	1.18	15.38	27.87	2.34
F-7	0.66	0.75	1.13	12.00	26.98	2.23
F-8	0.68	0.79	1.16	13.92	27.31	2.74
F-9	0.69	0.78	1.13	11.53	27.87	2.67
F-10	0.71	0.81	1.14	12.34	26.90	2.54
F-11	0.70	0.79	1.12	11.39	26.65	2.43

2.3 Drug- Excipients interaction study using DSC

The compatibility of the excipients with metformin hydrochloride, pioglitazone hydrochloride and glimepride were studied by subjecting the blend of different excipients with metformin hydrochloride, pioglitazone hydrochloride and glimepride to accelerated thermal stability at 40^0C /75% pH for 4 weeks and at 60^0C for 4 weeks. Drug- Excipients interaction study was done by using DSC.

1-2 mg of sample was heated in the aluminum disc over the range of 50-300°C at the rate of 20°C per minute and DSC spectra was recorded using TA 60W software. The obtained spectra were then studied for the interaction between drug and the excipients.



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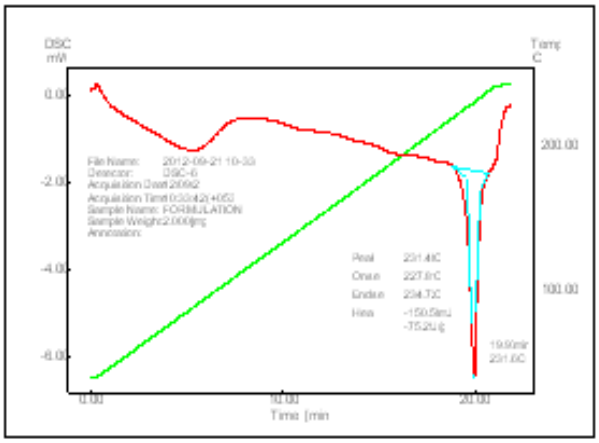

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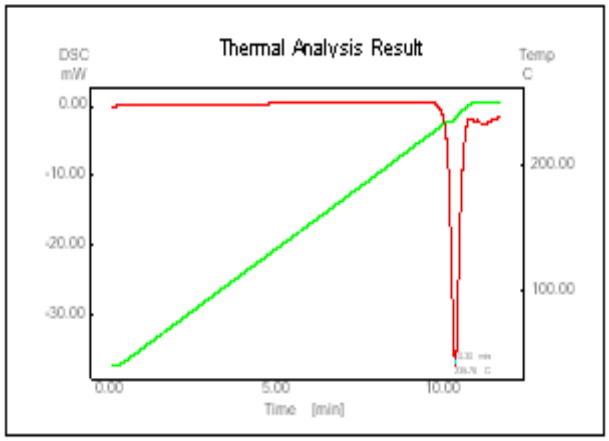

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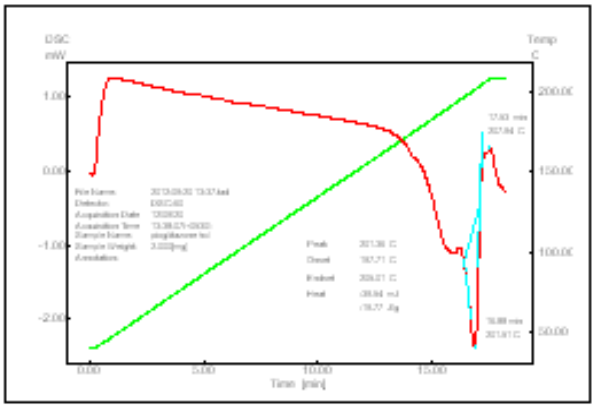

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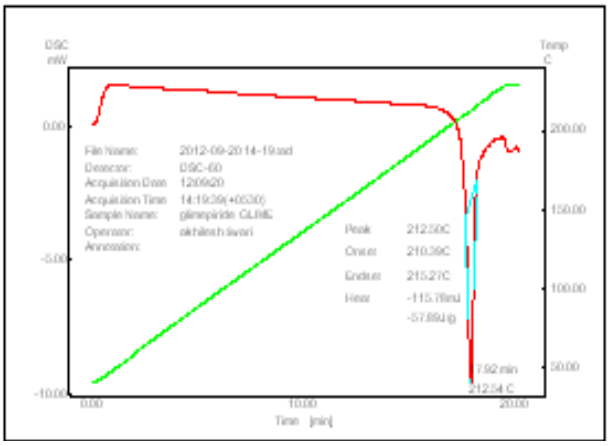


(e)

Figure 1: DSC of (a) blend of IR layer (b) blend of floating layer (c) Metformin HCl (d) Pioglitazone HCl (e) Glimiperide

2.4 Blends of IR layer

The IR layer was prepared by conventional dry granulation method. The weight of the IR layer was fixed to 170 mg. Glimepride, Pioglitazone, sodium starch glycolate were shifted through mesh (60#) and red iron oxide were passed through a mesh (100 #) and blended in a blender for 10 minutes at 24 RPM, so that the distribution of red iron oxide throughout the mass was uniform. Lactose DCL 15, microcrystalline cellulose pH 102 were sifted through 40 # and added to above blend in blender and mix for 5 minutes at 24 RPM. Magnesium stearate was sifted through 40 # and mix to above blend in blender for 3 minutes at 24 RPM. Composition of the IR layer is given in (Table 2).

Table 2: Formulation of immediate release layer of the bi layer tablet

S. No	Ingredient	mg/tablet		
		I.R.-1	I.R.-2	I.R.-3
1	Pioglitazone Hydrochloride	15.0	15.0	15.0
2	Glimepiride	1.0	1.0	1.0
3	Microcrystalline cellulose PH 102	90.0	90.0	90.0
4	Lactose DCL 15	39.0	49.0	53.0
5	Sodium starch glycolate	12.0	12.0	8.0
6	Red iron oxide	1.0	1.0	1.0
7	Magnesium Stearate	2.0	2.0	2.0
Total weight		170	170	170

2.5 Granulation of SR Layer

The SR layer was prepared by conventional wet granulation method. Different excipients like HPMC K4M, HPMC K15M, HPMC K100M, Sodium bicarbonate, Sodium carboxy methyl cellulose, Citric acid, Carbopol 934, Psyllium husk, metformin hydrochloride in different quantities in different formulations was used. All ingredients were sifted through 40 # mixed in blender for 5 minutes at 24 RPM, then the binding was done and granules were prepared by shifting the wet mass through mesh 20 # prepared granules

were dried in hot air oven at 45ºC for 1hour. Sift talc through 40 # and mix with above blend for 5 minutes in blender at 24 RPM. Sift Magnesium Stearate through 40 # and mix with above blend for 3 minutes in blender at 24 RPM. Composition of the SR layer is given in (Table 3).

Table 3: Formulation of floating SR layer of the bi layer tablet

S. No	Ingredient	mg/tablet										
		F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11
1	Metformin Hydrochloride	500	500	500	500	500	500	500	500	500	500	500
2	Psyllium Husk	60	30	10	10	-	-	-	-	-	-	-
3	HPMC K 4 M	-	-	-	-	100	100	-	-	-	-	-
	HPMC K 15 M	-	-	-	-	-	-	80	100	100	100	100
4	HPMC K 100 M	50	50	50	100	-	-	-	-	-	-	-
5	HPMC K 100 LV	-	-	-	53	58	51	51	51	51	51	46
6	Carbopol 934	-	-	-	-	50	40	40	30	30	30	30
7	Citric Acid	-	-	-	15	15	30	30	30	30	30	30
8	Sodium Carboxy Methyl Cellulose	-	-	-	-	-	-	-	-	40	30	25
9	Sodium bicarbonate	60	60	60	30	30	30	30	30	30	30	30
10	Betacyclodextrin	100	100	100	100	-	-	-	-	-	-	-
11	Cross povidone	201	201	198	-	-	-	-	-	-	-	-
12	PVP K 30	27	27	-	-	27	27	27	27	27	27	27
13	Talc	5	5	5	5	5	5	5	5	5	5	5
14	Magnesium Stearate	7	7	7	7	7	7	7	7	7	7	7
Total weight		1010	980	930	820	790	760	790	800	820	810	800

2.6 Floating lag time

The *in-vitro* floating behavior was studied by placing them in 1000 ml glass beaker filled with 500 ml of 0.1 N HCl pH 1.2 temperature 37.5 ^{0}C ± 0.5 ^{0}C. The floating lag time is the time period between placing the tablet in medium and time of tablet floating in media. The results are included in (Table 8).

2.7 Water uptake study (determination of swelling index):

The swelling of the polymers can be measured by their ability to absorb water and swell. The swelling property of the formulation was determined by various techniques.[11,12] The water uptake study of the tablet was done using USP dissolution apparatus II. The medium used was distilled water, 900 ml rotated at 50 rpm. The medium was maintained at 37±0.5 ◦C throughout the study. After a selected time intervals, the tablets were withdrawn, blotted to remove excess water and weighed. Swelling characteristics of the tablets were expressed in terms of water uptake by using following formula [13].

Swelling Index (S.I.) = {(Wt- Wo)/Wo}×100

Where; S.I. = swelling index, Wt = weight of tablet at time t, Wo = weight of tablet before immersion.

2.8 Dissolution study

An *in vitro* drug release study of the prepared bilayered gastro retentive tablets was determined using the USP I (basket) apparatus. With 900 ml of pH of 1.2 with 0.1% w/v sodium lauryl sulphate was used as dissolution media and maintained at 37±0.5ºC at a rotational speed of 100 rpm, for 60 min. followed by phosphate buffer pH 6.8 for 12hrs.

The sample was withdrawn at predetermined time interval 5, 10, 15, 30, 45, 60 min. for pioglitazone hydrochloride and glimiperide (immediate release layer) and 1, 2, 3, 4, 6, 8, 10, 12 hrs for metformin hydrochloride(sustained release floating layer). Dissolution Samples were analyzed by HPLC method.

The dissolution data obtained were plotted as percent cumulative drug release versus square root of time as per Higuchi equation.

$$Q = Kt^{1/2} \quad \text{------(1)}$$

The release data were further treated by the Ritger and Peppas equation. The equation was treated logarithmically to determine the value of release exponent, *n*; the value of *n* is indicative of mechanism of drug release.

$$\frac{Mt}{M\infty} = Kt^{n} \quad \text{------(2)}$$

2.9 HPLC Method Chromatographic conditions

Table 4: Final chromatographic condition for estimation of Metformin hydrochloride, Pioglitazone hydrochloride and Glimiperide

S. No	Parameter	Condition
1	Column	ODS, 5 µm, (250 X 4.6) mm
2	Mobile phase	Buffer: ACN (55:45 % v/v)
3	pH	5.0
4	Flow rate	1.0 ml/min
5	Wavelength of detection	230 nm
6	Detector	PDA

3. RESULT AND DISCUSSION:

The objective of the present investigation was to formulate and evaluate Hydro dynamically balanced bi-layered tablets of metformin hydrochloride, pioglitazone hydrochloride and glimiperide. Bi-layered tablet was prepared in which glimeperide and pioglitazone hydrochloride is in immediate release layer and metformin hydrochloride as floating sustained release layer, which can be retained in stomach for longer time with an overview to develop a once daily formulation for increased patient compliance and better clinical results, Immediate action of glimepiride and pioglitazone hydrochloride will be helpful to control excess sugar, which will be maintained by metformin hydrochloride action later on. Thus, the developed single tablet will be sufficient instead of two to three tablets of both drugs per day, and it will also increase patient compliance and therapeutic efficacy.

The compression force has a significant effect on in vitro drug release as well as on floating and swelling characteristics. So all the developed formulations were compressed at the compression force 7-8 kg/cm^2. The weight loss in the friability test was less then 1% in all the cases, all the formulations pass the weight variation test as the weight variation was found within pharmacopoeial limit of 5%.

Table 5: Average weight, weight variation, hardness, friability

Formulation	Average weight (mg/tab)	Weight variation	Hardness (Kg/cm^2)	Friability (%)
F-1	1180	Complies	11.0	0.11
F-2	1150	Complies	11.0	0.18
F-3	1000	Complies	11.0	0.22
F-4	990	Complies	11.0	0.24
F-5	960	Complies	10.0	0.29
F-6	930	Complies	10.0	0.35
F-7	940	Complies	10.0	0.38
F-8	950	Complies	10.0	0.32
F-9	990	Complies	10.0	0.19
F-10	980	Complies	10.0	0.24
F-11	970	Complies	10.0	0.27
MRKT	1115	Complies	10.0	0.28

3.1 Drug Release Study:

An *in vitro* drug release study of the prepared bilayered gastro retentive tablets was determined using the USP I (basket) apparatus. With 900 ml of pH of 1.2 with 0.1% w/v sodium lauryl sulphate was used as dissolution media and maintained at 37±0.5ºC at a rotational speed of 100 rpm, for 60 min. followed by phosphate buffer pH 6.8 for 12hrs. Dissolution Samples were analyzed by HPLC method.

Comparative in vitro release of drug from various formulations of floating layer having different concentration of excipients is shown in (Figure 3). psyllium husk was initially added as viscosity enhancer because of its gel forming character with β cyclodextrin as matrix former (F-1 to F-4) but these trails were not successful so in further development of formulations the psyllium husk and β cyclodextrin was totally replaced by HPMC K4M and carbopol but it was found that on immersion in 0.1 N HCl solution the tablet is buoyant without sedimentation (shows floating lag time 0 sec.). It might be due to the higher concentration of carbopol. Therefore in F-6 quantity of carbopol was reduced which improves floating lag time, but drug release was not found satisfactory (more than 70% in fourth hours). So in next trail (F-7) HPMC K 4M was replaced with HPMC K15M which impart a positive but not satisfactory effect on drug release as well as there is no significant effect on drug release by increasing the concentration of HPMC K15M (F-8). The percent cumulative drug release for the formulation (F-9) containing sodium carboxy methyl cellulose (Na. CMC) is slower which might be due to gel formation characteristics of sodium carboxy methyl cellulose which contributes in slower release in latter hours. As the concentration of sodium carboxy methyl cellulose reduced (F-10, F-11) there is a significant improvement on the drug release profile respectively. Therefore formulation 11 (F-11) was taken in consideration.

Table 6: Percent drug release from immediate release layer

TIME (Min)	% Drug Release Pioglitazone hydrochloride	% Drug Release Glimepride
5	72.06%	56.22%
10	78.85%	61.54%
15	86.34%	74.31%
30	91.23%	88.11%
45	97.15%	92.32%
60	98.33%	93.45%

Table 7: Percent drug release from gastro retentive sustained release layer

TIME	% Drug Release metformin hydrochloride							
	F-5	F-6	F-7	F-8	F-9	F-10	F-11	MRKT
0.5	17.34	28.10	26.40	26.20	17.33	20.63	21.27	19.34
1	26.42	39.50	39.10	38.34	27.05	31.69	32.59	32.23
2	36.91	51.52	50.01	49.00	34.19	37.88	39.84	38.90
3	43.26	65.91	69.20	62.84	45.12	45.25	46.28	45.78
4	49.01	74.60	73.01	70.15	52.30	49.89	52.28	53.40
6	59.24	83.01	82.23	79.85	64.45	66.03	67.49	68.12
8	69.40	90.73	89.14	88.91	72.81	77.11	78.36	77.89
10	77.14	96.12	95.32	94.36	81.62	89.00	93.71	94.54

12	83.23	99.06	99.60	99.12	86.10	94.98	97.67	96.12

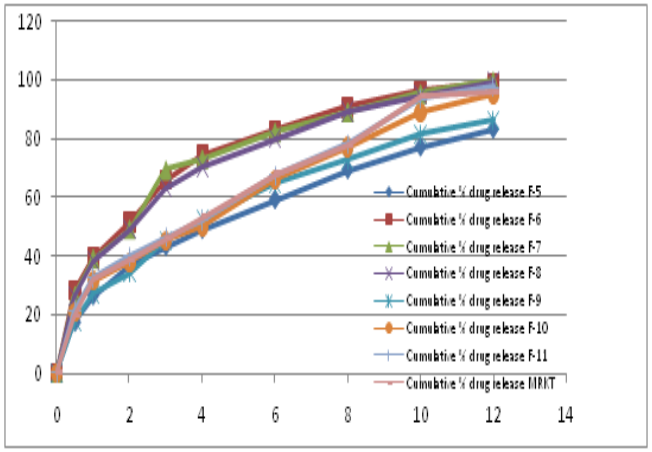


Figure 2: Effect of different excipients on drug release from floating layer of tablet

As concentration of carbopol is decreased (F-5, F-6, F-7) initial burst effect is increased in first hour. Which can be seen in cumulative % drug release from 17.34 to 28.10 and 26.40 respectively in first hour. This is due to the fact that carbopol has pKa 6 which remains unionized in acidic environment of dissolution medium. Therefore it acts as a physical barrier to drug release from the formulation. The maximum burst effect is seen in F-6 (28.10 %) which was further controlled by replacing HPMC K4M with HPMC K15M (F-7) 26.10%. This might be due to increase in diffusion path length for the drug which may retard drug release from the formulation, but it was found that HPMC alone was unable to control release of drug in last hours, so combination of polymer & gel forming agent (Na. CMC) which produce gel network to polymeric matrix system, is able to arrest drug release from the formulation (F-9). The quantity of Sodium CMC was further decreased to get desirable drug release. It is also reported that citric acid level greatly influences the drug release and floating lag time of the formulation.

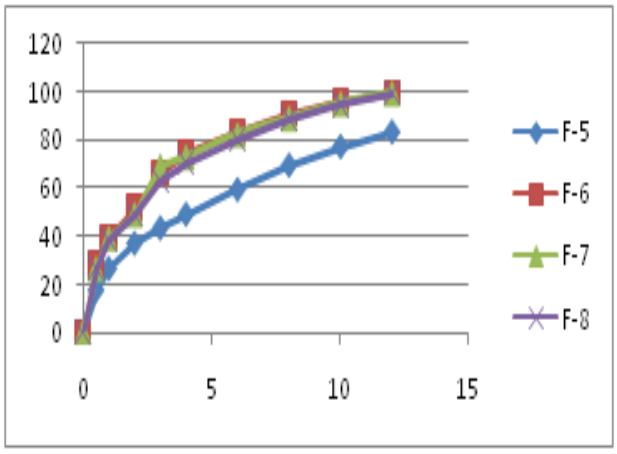


Figure 3: Effect of Carbopol on drug release from floating layer

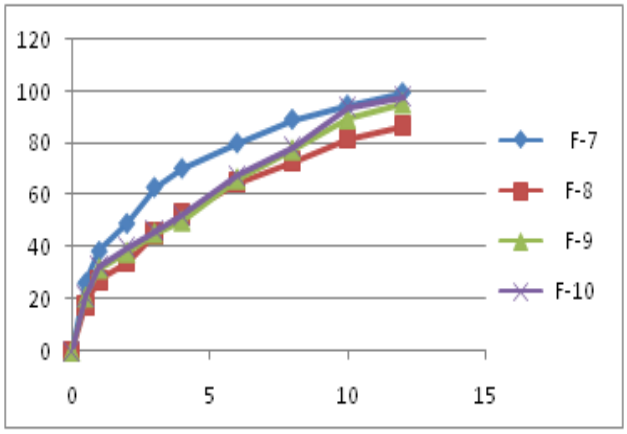


Figure 4: Effect of Na. CMC on drug release from floating layer

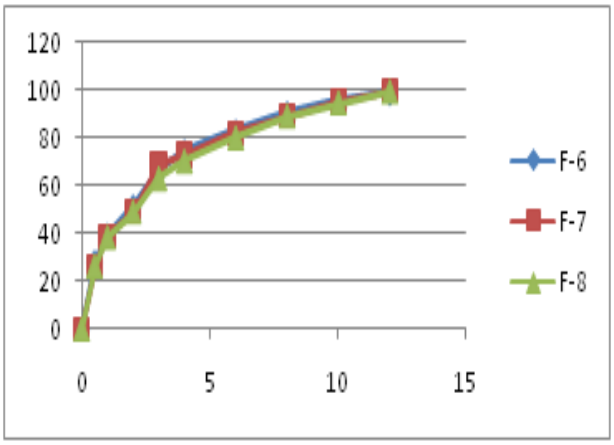


Figure 5: Effect of HPMC on drug release from floating layer

3.2 Water uptake study

On immersion in 0.1 N HCl solutions at pH 1.2 at 37±0.5ºC tablet floats immediately and remains buoynant upto 8-12 hours without disintegration. The floating property of table is governed by swelling of polymer when it comes in contact with the gastric fluid, which in turn results in increase in the bulk volume, and presence of internal voids in dry centre of the tablet.

The percentage swelling of the tablet was determined at different time intervals. The formulation 5 shows highest swelling index due to presence of highest amount of carbapol. As the amount of carbopol decreased (F-6), swelling index was also found to be decreased, in F-7 swelling index is increased due to use of higher viscosity grade HPMC (HPMC K 15 M). Swelling index was also found to be increased in F-8 due to increase in quantity of HPMC K 15 M. but in F-8, F-9, F-10, swelling index is decreased due to presence of sodium CMC. It was also found that as the concentration of sodium CMC is decreased, swelling index was found to be increased. So from overall study, it was concluded that swelling increase as the time passes, because

the polymer gradually absorb water due to hydrophilicity of polymer. The outermost hydrophilic polymer hydrates, swell and a gel like barrier is formed at outer surface. As the gelatinous layer progressively dissolves, the hydration swelling release processes continuous towards new exposed surface. So the viscosity of polymer has major influence on swelling process. Hence, from results it can be concluded that linear relationship exists between swelling process and viscosity.

Table 8: Floating lag time & Swelling Index

Batch No	Time in minutes	Swelling Index
F-1	Not floating	Not observed
F-2	Not floating	Not observed
F-3	Not floating	Not observed
F-4	Not floating	Not observed
F-5	1.1	213
F-6	3.5	240
F-7	2.8	233
F-8	4.1	252
F-9	3.7	228
F-10	2.4	236
F-11	2.2	240

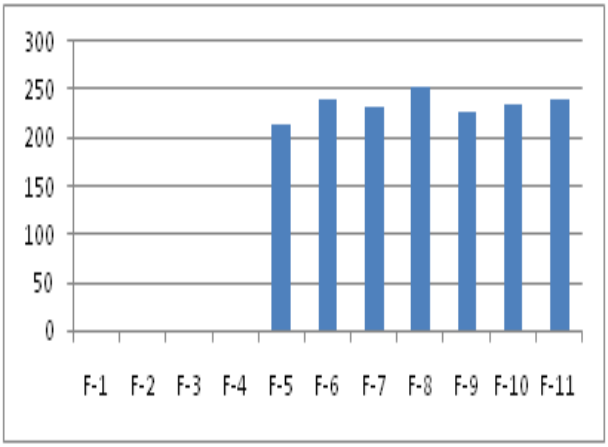
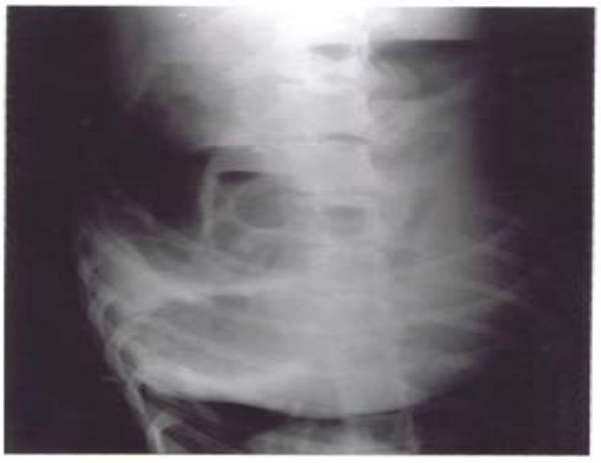


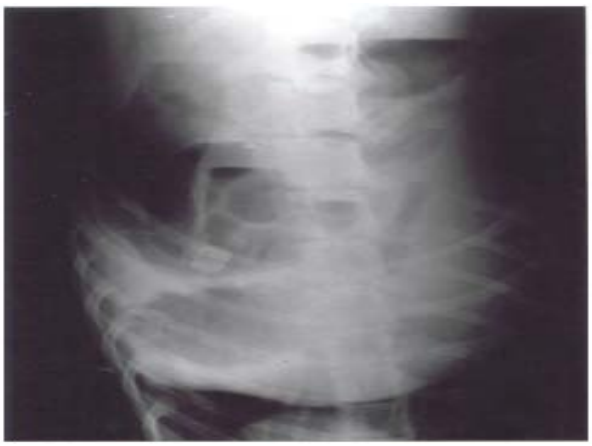
Figure 6: Swelling Index of the developed formulation

3.3 *In vivo* floating behavior

The *in vivo* floating behavior was investigated by X-Ray photographs of stomach of dog, administered tablet laden with barium sulphate at periodic time intervals. The study indicated a total gastric residence time (GRT) of about 4.5 h.



X-ray of dog's empty stomach



After 4.5 hour of administration of tablet

Figure 7: *In vivo* floating behavior in dogs stomach

3.4 Analysis of the drug release data

The drug release data were explored for the type of release mechanism followed. The data were treated with different equations for all developed formulations i.e., zero order, first order, higuchi & Peppas model. Correlation coefficient value of all formulation did not follow fair zero order release pattern and correlation coefficient was found 0.804-0.934. When data were plotted according to the first order equation, the formulation showed a fair linearity, with correlation coefficient values between 0.914-0.998. Release of the drug from floating matrix tablet containg hydrophilic polymers generally involves factors of diffusion. Diffusion is related to the transport of drug from the doses matrix into the *in vitro* studies which depends on the concentration. As gradient varies, the drug is released & the distance for diffusion increased. This could explain why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred as square root kinetics or Higuchi's kinetics. In this experiment, the *invitro* release; profile of the drug from all the plots Showed high linearity (0.963-0.998). This represents the release process under the drug diffusion through polymer matrix, and it was found that the passage of drug through the hydrated gel matrix tablet is depends on the square root of time, a linear relationship was observed with the regression coefficient close to 1 which indicate that the formulation is follows higuchi equation of release kinetics.

Table 9: Correlation coefficient of different mathmetical models

Formulation	Higuchi	First order	Zero order	Corsemeyer
F-5	0.998	0.996	0.911	0.956
F-6	0.966	0.963	0.804	0.869
F-7	0.963	0.990	0.805	0.921
F-8	0.978	0.928	0.833	0.941
F-9	0.997	0.998	0.912	0.958
F-10	0.993	0.951	0.934	0.96
F-11	0.992	0.914	0.934	0.959
F-MRKT	0.991	0.932	0.930	0.96

3.5 Calculation of F2 value:

The purpose of F2 value calculation is to be able to compare entire curves and not time points. F2 value between 50 and 100 signifies that the two dissolution profiles are similar. F2 values for the formulations (F1-F11) The similarity factor for F4, F5, F6, F7, F8, F9, F10 and F11 lies above 50, which indicated a similar dissolution profile of these formulations with that of reference (MRKT). The F2 value amongst the prepared formulations was maximum for F11 (71.72), hence this formulation was chosen for *in vivo* studies.

3.6 Stability studies:

The test formulation (F-11) subjected to stability studies ($40^{O}C$/ 75% RH) for a period of 90 days. The results are shown in Table no. 31 from the data it is evident that there was no significant degradation of drugs in the tablet, as the physico-chemical characteristics of the tablets remained unaltered during the stability study.

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