Advance Research in Pharmaceuticals and Biologicals

(A Peer Reviewed International Journal for Pharmaceutical and Allied Research)

ISSN 2250-0774 USA CODEN: ARPBGZ

FORMULATION AND *IN VITRO* EVALUATION OF FLOATING DRUG DELIVERY SYSTEM OF PERINDOPRIL ERBUMINE TABLETS

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Received on 02/09/2018 Revised on 07/09/2018 Accepted on 09/09/2018

ABSTRACT

The objective of this study was to formulate and evaluate a Gastric oral floating tablets of Perindopril Erbuminen. Twelve formulation containing hydrophilic polymers that are hydroxy propyl methyl cellulose K4M, hydroxy propyl methyl cellulose K100M and Xanthan Gum, gas generating agent, sodium bi carbonate were used. The tablet were compressed and evaluated with different parameters like angle of repose, Carr's index diameter thickness, average weight, hardness, friability, drug content, invitro buoyancy study and kinetic drug release data. The tablets remained buoyant over 8 hours in the release medium. The amount of sodium bi carbonate found to be significant for not only to remaining buoyant without causing disintegration of the tablet, but also to release of drug in acidic medium and solubilizing agent amount found to be significant as for as the release of the drug is concern from the twelve formulation. F8 is a best formulation to determine the mode of release, the data was subjected to higuchi's model.

KEYWORDS: Floating drug delivery system, controlled drug release, Perindopril Erbumine, Hydroxy propyl methyl cellulose K4M.

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INTRODUCTION

Oral administration is the most convenient mode of drug delivery and is associated with superior patient compliance as compared to other modes of drug intake. However, oral administration has only limited use for important drugs, from various pharmacological categories, that have poor oral bioavailability due to incomplete absorption and/or degradation in the gastrointestinal (GI) tract. Some of these drugs are characterized by a narrow absorption window (NAW) at the upper part of the gastrointestinal tract. This is because of proximal part of the small intestine exhibits extended absorption properties (including larger gaps between the tight junctions, and dense active transporters). Despite the extensive absorption properties of the duodenum and jejunum, the extent of absorption at these sites is limited because the passage through this region is rapid. Enhancing the gastric residence time (GRT) of a NAW the drug may significantly improve the net extent of its absorption.[1,2]Floating drug delivery systems can remain in the gastric region for several hours 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 a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

Floating systems or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and 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 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 the fluctuations in plasma drug concentration.[3,4]

Drug Details

MATERIALS AND METHODS [5,6,7]

Perindopril Erbumine was a gift sample from (Aurobindo Pharmaceuticals Limited, Hyderabad, India). HPMC K4M and HPMC K100M were obtained from Hetro Pharmaceuticals, Hyderabad, India). Sodium bicarbonate, Citric acid, Magnesium stearate was procured from Loba chemie Private Ltd. All other chemicals and reagents were analytical grade and used as received.

Fourier Transform Infrared (FTIR) spectroscopy:

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany(Alpha T).The solid powder sample directly place on yellow crystal which was made up of ZnSe. The spectra were recorded over the wave number of 4000 cm^{-1} to 550 cm^{-1}.

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Formulation development of floating Tablets:

For optimization of sodium bicarbonate concentration, granules were prepared by direct compression method. Drug and all other ingredients were individually passed through sieve no ≠ 60.All the ingredients were mixed thoroughly by triturating up to 15 min.The powder mixture was lubricated with talc.The tablets were prepared by using direct compression method by using 6 mm punch.

Table 1 : Formulation composition for Floating tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Perindopril Erbumine	8	8	8	8	8	8	8	8	8	8	8	8
HPMC K4M	4	8	12	16	-	-	-	-	-	-	-	-
HPMC K100M	-	-	-	-	4	8	12	16	-	-	-	-
Xanthan gum	-	-	-	-	-	-	-	-	4	8	12	16
Sodium bicarbonate	10	10	10	10	10	10	10	10	10	10	10	10
Citric acid	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium Stearate	3	3	3	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Mannitol	67	63	59	55	67	63	59	55	67	63	59	55
Total weight	100	100	100	100	100	100	100	100	100	100	100	100

Evaluation of post compression parameters for prepared Tablets [8,9,10,11]

The designed compression tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test:

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Hardness:

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness:

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability:

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Pre weighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re-weighed, and loss in the weight of tablet is the measure of friability and is expressed in percentage as

% Friability = [(W1-W2) / W1] × 100

Where, W1 = Initial weight of tablets

W2 = Weight of the tablets after testing

Determination of drug content:

Both compression-coated tablets of were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of clopidogrel were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

In vitro Buoyancy studies:

The in vitro buoyancy was determined by floating lag time, and total floating time. (As per the method described *by Rosa et al*) The tablets were placed in a 100ml beaker containing 0.1N HCL. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and duration of time the tablet constantly floats on the dissolution medium was noted as Total Floating Time respectively (TFT).

In vitro drug release studies

900ml 0f 0.1 HCL was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c $\pm$ 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 12 hours and then the medium 0.1 N HCL was taken and process was continued from 0 to 12 hrs at 50 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with media and analyzed by spectrophotometrically at 387 nm using UV-spectrophotometer.

Application of Release Rate Kinetics to Dissolution Data [12,13,14]:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics:

To study the zero–order release kinetics the release rate data ar e fitted to the following equation.

$F = K_o t$

Where, 'F' is the drug release at time't', and 'K_o' is the zero order release rate constant. The plot of

% drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation

Log (100-F) = kt

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

F = k t1/2

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model:

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer-Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$M_t/ M_\infty = K t^n$$

Where, M_t/ M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for supercase II transport, n > 1. In this model, a plot of log (M_t/ M_∞) versus log (time) is linear.

RESULTS AND DISCUSSION

Drug – Excipient compatability studies

Fourier Transform-Infrared Spectroscopy:

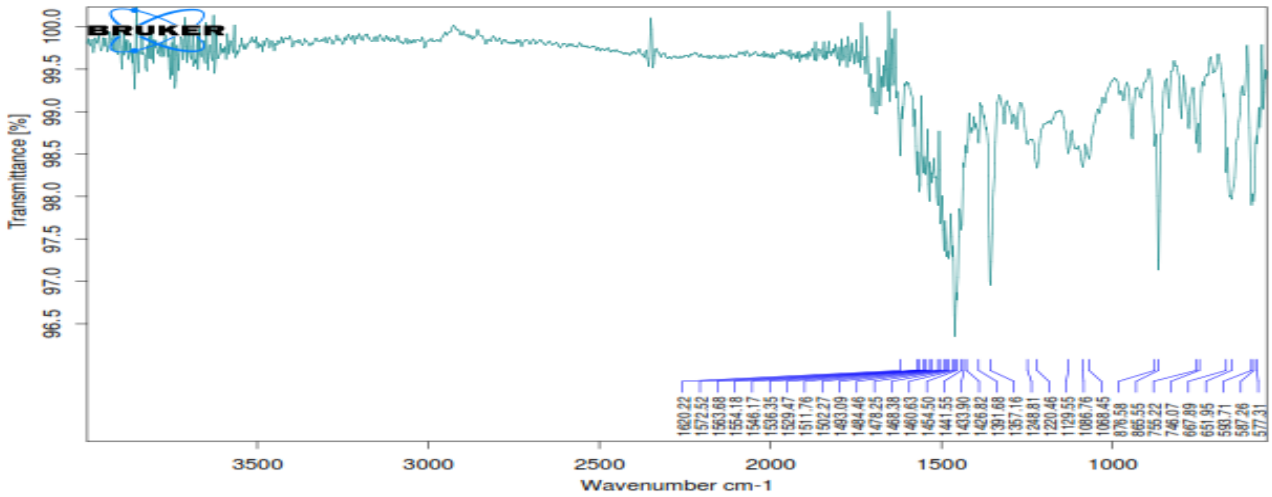


Figure 1 : FTIR Spectrum of pure drug

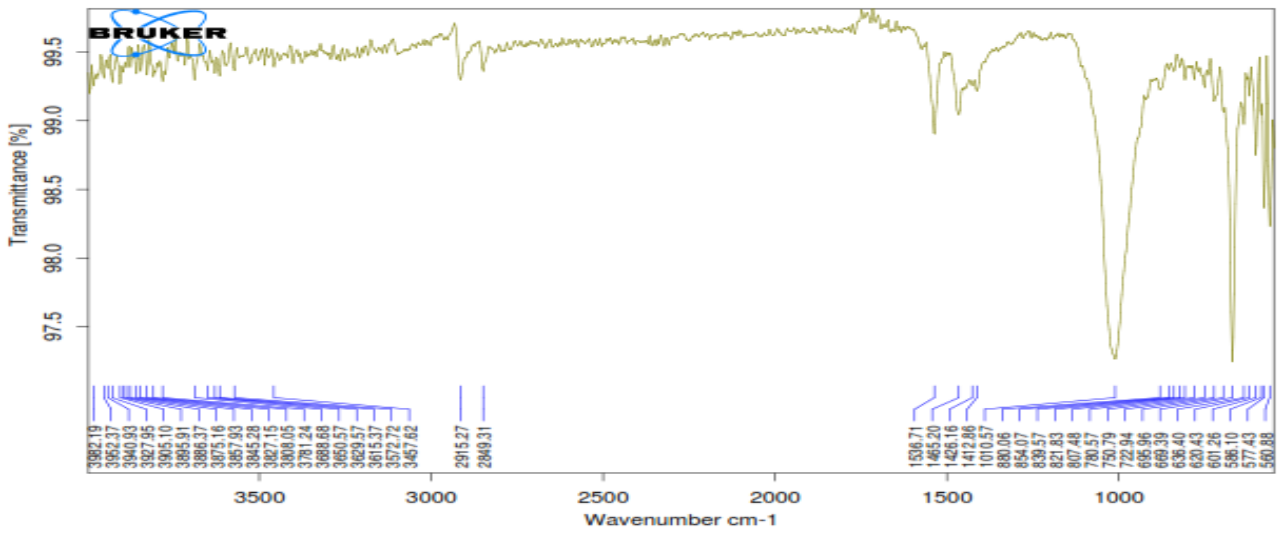


Figure: 2 FTIR Spectrum of optimised formulation

There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions.

Perindopril Erbumine are also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug.

Preformulation parameters of powder blend:

Table 2 : Pre-formulation parameters of blend

Formulation Code	Angle of Repose	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's Ratio
F1	24.20±1.0	0.33±0.0	0.416±0.00	20.10±1.52	1.25±0.019
F2	26.62±0.98	0.316±0.00	0.365±0.01	16.32±0.11	1.19±0.00
F3	21.36±0.82	0.317±0.01	0.372±0.00	13.58±0.92	1.170±0.013
F4	27.89±0.80	0.348±0.01	0.416±0.01	16.27±0.039	1.19±0.022
F5	19.08±0.72	0.345±0.01	0.442±0.01	18.24±0.16	1.22±0.001
F6	21.62±0.53	0.342±0.012	0.380±0.00	21.89±0.56	1.23±0.021
F7	26.89±0.92	0.319±0.024	0.377±0.00	16.62±0.32	1.201±0.019
F8	28.47±0.92	0.334±0.01	0.4527±0.00	19.88±0.33	1.24±0.04
F9	28.97±0.86	0.3330±0.01	0.410±0.01	20.24±1.49	1.26±0.019
F10	27.78±0.78	0.362±0.01	0.4712±0.01	20.82±0.07	1.28±0.07
F11	28.58±0.94	0.334±0.01	0.428±0.003	22.16±1.20	1.30±0.09
F12	24.62±0.90	0.325±0.00	0.399±0.00	17.20±0.12	1.21±0.02

powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.33 to 0.362 (gm/ml) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.365 to 0.471showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 18 which shows that the powder has good flow properties. All the formulations has shown the hausners ratio ranging between 1.19 to 1.170 indicating the powder has good flow properties.

Quality Control Parameters For tablets:

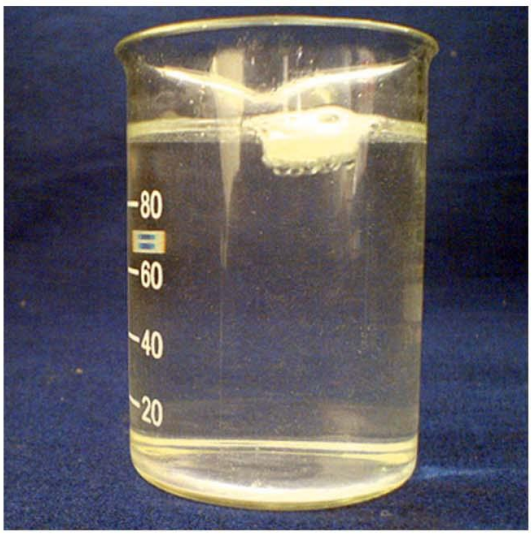
Tablet quality control tests such as weight variation, hardness, and friability, thickness, Drug content and drug release studies were performed for floating tablets. All the parameters for Floating Tablets such as weight variation, friability, hardness, thickness, drug content were found to be within limits.

In-vitro buyoncy Study In-vitro buoyancy studies conducted the gas generated id trapped and protected with in the gel formed by hydration of polymer. The floating lag time was in range of 38sec to 47 sec also tablets remained buoyant for a period of 12 hours

At initial time

After 5 seconds

After 50 seconds



After 2 minutes

After 12 hours

***Table 3: In vitro* quality control parameters**

Formulation codes	Average Weight (mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Total Floating Time (hrs)	Floating Lag time (sec)
F1	99.07±0.08	5.8±0.86	0.58±0.21	2.3±0.8	98.84	6	42
F2	98.08±0.06	5.5±0.37	0.56±0.28	2.1±0.17	96.59	7	45
F3	99.24±0.24	5.3±0.68	0.53±0.34	2.4±0.24	98.88	8	44
F4	100.34±0.45	4.9±0.74	0.57±0.19	1.8±0.39	99.71	9	43
F5	97.18±0.68	5.1±0.95	0.57±0.55	2.0±0.84	95.28	7	41
F6	98.57±0.14	5.6±0.25	0.46±0.27	2.2±0.45	98.77	10	40
F7	95.39±0.65	5.0±0.67	0.59±0.95	2.0±0.67	9738	11	42
F8	97.76±0.74	5.7±0.89	0.48±0.17	2.1±0.88	99.47	>12	38
F9	98.28±0.28	5.3±0.93	0.57±0.28	2.6±0.51	96.53	12	45
F10	96.96±0.34	5.8±0.76	0.59±0.66	1.8±0.26	98.76	12	47
F11	99.84±0.22	5.6±0.67	0.48±0.38	2.5±0.18	97.83	12	42
F12	100.66±0.12	5.2±0.96	0.56±0.84	2.7±0.44	99.35	12	46

***In Vitro* Drug Release Studies**

Table 4: Dissolution data of Floating Tablets

TIME	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0		0	0	0	0	0	0	0	0
0.5	15.26	30.36	20.15	18.41	24.12	28.19	15.41	13.50	19.25	9.23	6.47	04.31
1	30.34	43.52	34.99	24.62	38.64	36.77	20.98	25.62	22.11	15.69	14.56	11.29
2	46.18	56.88	48.26	31.94	50.20	45.82	26.55	38.97	25.09	30.04	25.24	16.27
3	53.64	68.97	57.38	42.76	69.56	57.59	32.84	43.54	29.54	49.08	29.09	20.34
4	62.22	73.43	66.75	55.29	75.43	63.26	39.39	50.93	33.36	57.71	33.24	28.09
5	84.23	86.28	70.19	63.48	83.01	71.14	44.71	58.17	39.67	59.61	38.09	32.48
6	98.97	93.33	85.44	70.52	95.57	75.96	53.05	66.22	44.36	65.05	43.15	40.85
7		96.88	91.96	78.87	98.69	83.58	60.87	72.31	50.77	69.94	51.28	49.02
8			97.57	85.37		89.45	67.02	79.07	56.42	71.78	58.42	58.92
9				99.33		94.74	74.15	83.12	60.02	74.02	62.70	62.21
10						97.99	89.24	87.75	64.46	79.66	70.36	69.95
11							97.54	91.01	79.39	81.23	72.03	70.68
12								96.68	86.14	84.93	78.98	74.85

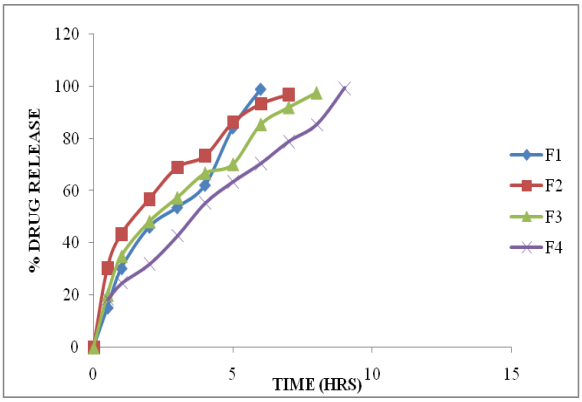


Figure 4 : Dissolution data of Perindopril Erbumine Floating tablets containing HPMC K4M

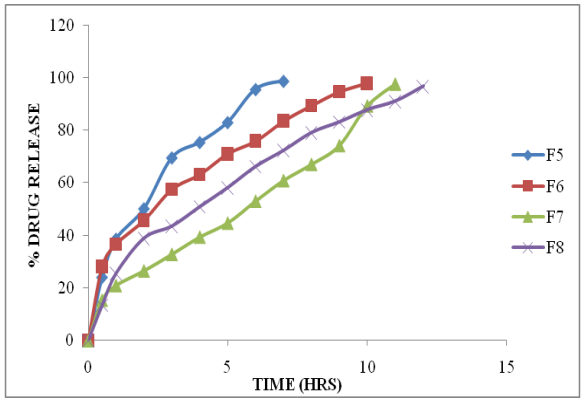


Figure 5: Dissolution data of Perindopril Erbumine Floating tablets containing HPMC K100M

Application of Release Rate Kinetics to Dissolution Data for optimised formulation:

Table 5: Application kinetics for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM % RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
13.5	**0.5**	0.707	1.130	-0.301	1.937	27.000	0.0741	-0.870	86.5	4.642	4.423	0.219
25.62	**1**	1.000	1.409	0.000	1.871	25.620	0.0390	-0.591	74.38	4.642	4.206	0.436
38.97	**2**	1.414	1.591	0.301	1.786	19.485	0.0257	-0.409	61.03	4.642	3.937	0.704
43.54	**3**	1.732	1.639	0.477	1.752	14.513	0.0230	-0.361	56.46	4.642	3.836	0.805
50.93	**4**	2.000	1.707	0.602	1.691	12.733	0.0196	-0.293	49.07	4.642	3.661	0.981
58.17	**5**	2.236	1.765	0.699	1.621	11.634	0.0172	-0.235	41.83	4.642	3.471	1.170
66.22	**6**	2.449	1.821	0.778	1.529	11.037	0.0151	-0.179	33.78	4.642	3.233	1.409
72.31	**7**	2.646	1.859	0.845	1.442	10.330	0.0138	-0.141	27.69	4.642	3.025	1.616
79.07	**8**	2.828	1.898	0.903	1.321	9.884	0.0126	-0.102	20.93	4.642	2.756	1.886
83.12	**9**	3.000	1.920	0.954	1.227	9.236	0.0120	-0.080	16.88	4.642	2.565	2.076
87.75	**10**	3.162	1.943	1.000	1.088	8.775	0.0114	-0.057	12.25	4.642	2.305	2.336
91.01	**11**	3.317	1.959	1.041	0.954	8.274	0.0110	-0.041	8.99	4.642	2.079	2.562
96.68	**12**	3.464	1.985	1.000		8.057	0.0103	-0.015	3.32	4.642	1.492	3.150

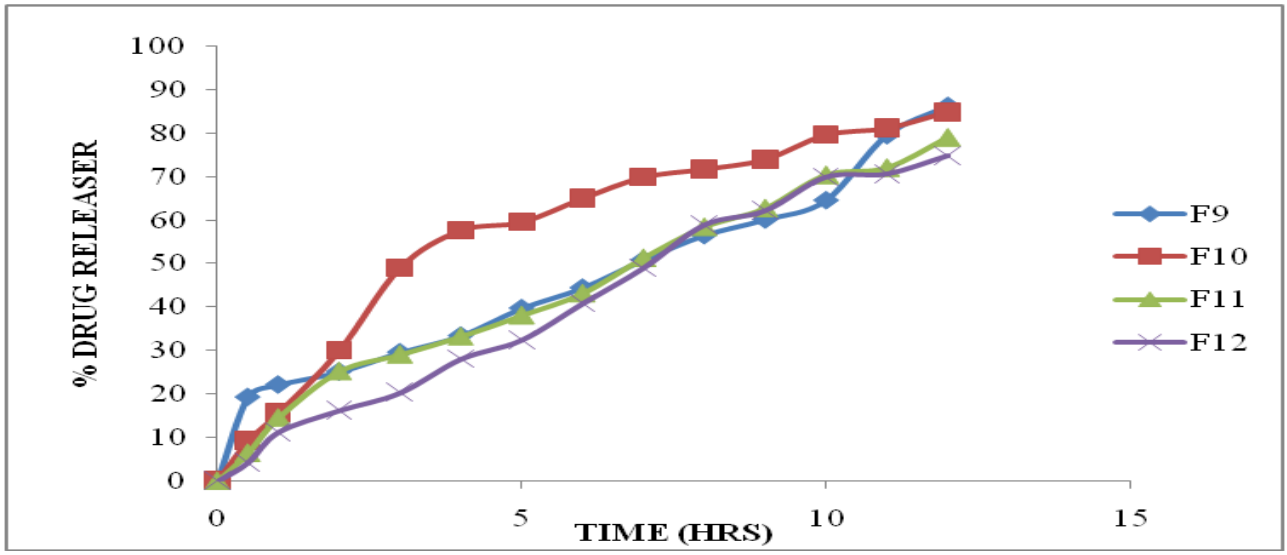


Figure 6: Dissolution data of Perindopril Erbumine Floating tablets containing Xanthan Gum

From the dissolution data it was evident that the formulations prepared with HPMC K4M as polymer were retarded the More drug release within 12 hours.

Whereas the formulations prepared with higher concentration of HPMC K100M retarded the drug release up to 12 hours. In lower concentrations the polymer was unable to retard the drug release. As it can be seen from (Figure) Polymeric system with low viscosity polymer (HPMC K4 M) yielded a faster initial burst effect except HPMC K100 M.

The formulations prepared with Xanthan Gum showed More retardation capacity hence they were not considered.

Hence from the above dissolution data it was concluded that F8 formulation was considered as optimised formulation because good drug release (96.68%) in 12 hours.

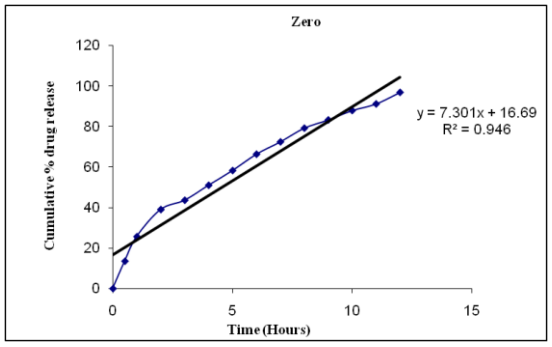


Figure 7: Zero order release kinetics

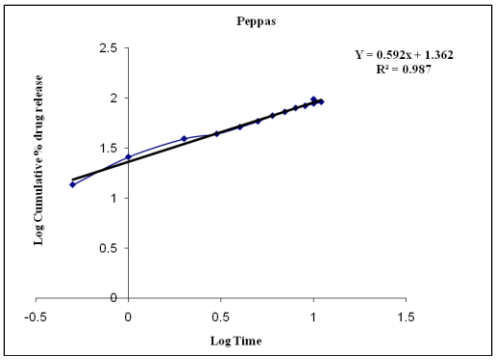


Figure 9 : Kors mayer peppas release kinetics

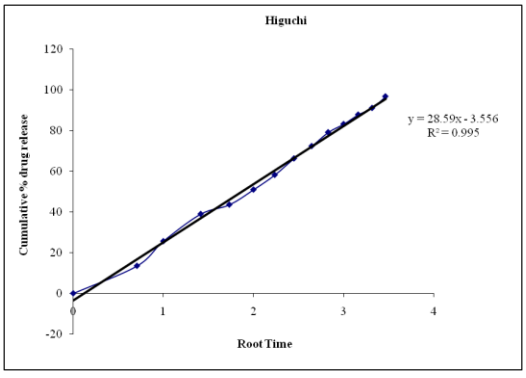


Figure 8 : Higuchi release kinetics

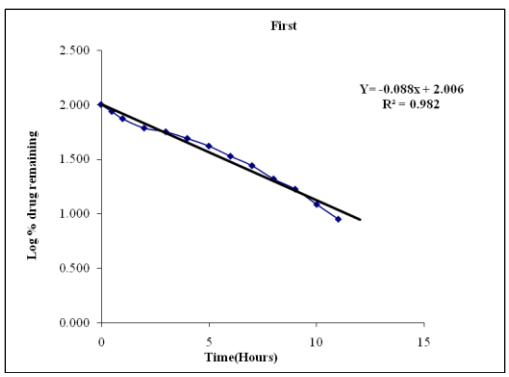


Figure 10 : First order release kinetics

Optimised formulation F8 was kept for release kinetic studies. From the above graphs it was evident that the formulation F8 was followed Higuchi release mechanism.

CONCLUSION

Gastric oral floating controlled drug delivery of perindopril Erbumine was prepared by HPMC k 4M, HPMC k 100M,and Xanthan Gum as polymers, solubilizing agent as PVP and gas generating agent sodium bicarbonate was used, proved to be an ideal formulation as it released the drug in controlled fashion for extended period of time by maintaining the buoyancy the formulations F8 was selected as an optimized formulation. The .controlled release floating drug delivery of perindopril Erbumine showed sufficient release for extended period of time. Frequent dosing and possible incomplete absorption of drug can be avoided. Further it also proves to be a very economical dosage form

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