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Formulation and invitro evaluation of effervescent floating tablets of perindopril

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ABSTRACT

The purpose of this research was to formulate and evaluate the Floating sustained release tablets of Perindopril 4mg, Perindopril is a medication used to treat high blood pressure, heart failure, or stable coronary artery disease. The floating tablets were based on effervescent approach using sodium bicarbonate a gas generating agent. All formulations were evaluated for the pre compression and post compression, *In vitro* buoyancy, *In vitro* dissolution studies. Pre-compression studies revealed that there was no sign of any interaction between drug and polymers and all formulation showed good flow properties. Results of post compression parameters were found within the limits for all formulations. Among all the formulation F6 showed better buoyancy and drug release profile. The release of drug from the prepared formulations (F6) was found to follow zero order and mechanism

Key words: Perindopril, Carbapol 934, HPMC K 100, Eudragit RSPO and Floating tablets.

INTRODUCTION

Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT).[1] Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment[2] Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Over the last few decades, several gastroretentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach[3] , low density (floating) systems that causes buoyancy in gastric fluid[4,5,6], mucoadhesive systems that causes bioadhesion to stomach mucosa[7], unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach[8,9],superporous hydrogel systems[10] magnetic systems[11]etc. The current review deals with floating type gastroretentine drug delivery system.

Basic gastrointestinal tract physiology

The stomach is divided into 3 regions anatomically: fundus, body, and antrum pylorus. The proximal part is the fundus and the body acts as a reservoir for undigested material, where as the antrum is the main site for mixing

motions and acts as a pump for gastric emptying by propelling actions. Gastric emptying occurs during fasting as well as fed states but the pattern of motility is distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle through both stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is divided into following 4 phases.[12]

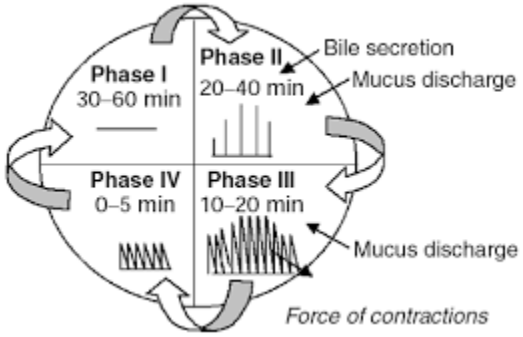

Figure 1: Schematic Representation of Interdigestive Motility

Phase I: This period lasts about 30 to 60 minutes with no contractions.

Phase II: This period consists of intermittent contractions that increase gradually in intensity as the phase progresses, and it lasts about 20 to 40 minutes. Gastric discharge of fluid and very small particles begins later in this phase.

Phase III: This is a short period of intense distal and proximal gastric contractions (4-5 contractions per minute) lasting about 10 to 20 minutes these contractions, also known as ''house-keeper wave,'' sweep gastric contents down the small Intestine.

Phase IV: This is a short transitory period of about 0 to 5 minutes, and the contractions dissipate between the last part of phase III and quiescence of phase

Need For Gastroretention

- Drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT).
- Drugs that are less soluble or that degrade at the alkaline pH.
- Drugs that are absorbed due to variable gastric emptying time.
- Local or sustained drug delivery to the stomach and proximal small intestine to treat certain conditions.
- Particularly useful for the treatment of peptic ulcers caused by H.Pylori infections.[12]

MATERIALS AND METHODS

Perindopril Provided by SURA LABS, Dilsukhnagar, Hyderabad. Carbapol 934 from Degussa India Ltd. (Mumbai, India). HPMC K 100 from Arvind Remedies Ltd, Tamil nadu, India. Eudragit RSPO from Merck Specialities Pvt Ltd, Mumbai, India. Citric acid from Laser Chemicals, Ahmedabad, India. Sodium bicarbonate from Merck Specialities Pvt Ltd, Mumbai, India. Micro crystalline cellulose from Merck Specialities Pvt Ltd, Mumbai, India. Magnesium Stearate from Apex Chemicals, Ahmedabad, India.Talc from S.D. Fine Chem., Mumbai, India.

METHODOLOGY

Analytical method development:
Determination of absorption maxima:

A solution containing the concentration 10 µg/ mL drug was prepared in 0.1N HCL UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

Preparation calibration curve

10mg Perindopril pure drug was dissolved in 10ml of methanol (stock solution1) from stock solution 1ml of solution was taken and made up with10ml of 0.1N HCL (100µg/ml). From this 1ml was taken and made up with 10 ml of 0.1N HCL (10µg/ml). The above solution was subsequently diluted with 0.1N HCL to obtain series of dilutions Containing 5, 10, 15, 20, 25µg /ml of per ml of solution. The absorbance of the above dilutions was measured at 230 nm by using UV-Spectrophotometer taking 0.1N HCL as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis.

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

Procedure for direct compression method:

1) Drug and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method by using 6mm punch.

Formulation of tablets

Table 1: Formulation composition for Floating tablets

INGREDIENTS (MG)	FORMULATION CODE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Perindopril	4	4	4	4	4	4	4	4	4
Carbapol 934	4	8	12	-	-	-	-	-	-
HPMC K 100	-	-	-	4	8	12	-	-	-
Eudragit RSPO	-	-	-	-	-	-	4	8	12
Citric acid	10	10	10	10	10	10	10	10	10
Sodium bicarbonate	8	8	8	8	8	8	8	8	8
Micro crystalline cellulose	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Magnesium Stearate	4	4	4	4	4	4	4	4	4
Talc	5	5	5	5	5	5	5	5	5
Total Weight	100	100	100	100	100	100	100	100	100

All the quantities were in mg

RESULTS AND DISCUSSION

Analytical Method

Determination of absorption maxima

The standard curve is based on the spectrophotometer. The maximum absorption was observed at 230nm.

b. Calibration curve

Graphs of Perindopril was taken in 0.1N HCL (pH 1.2)

Table no 2: Observations for graph of Perindopril in 0.1N HCL

Conc [µg/mL]	Abs
0	0
5	0.102
10	0.187
15	0.265
20	0.351
25	0.429

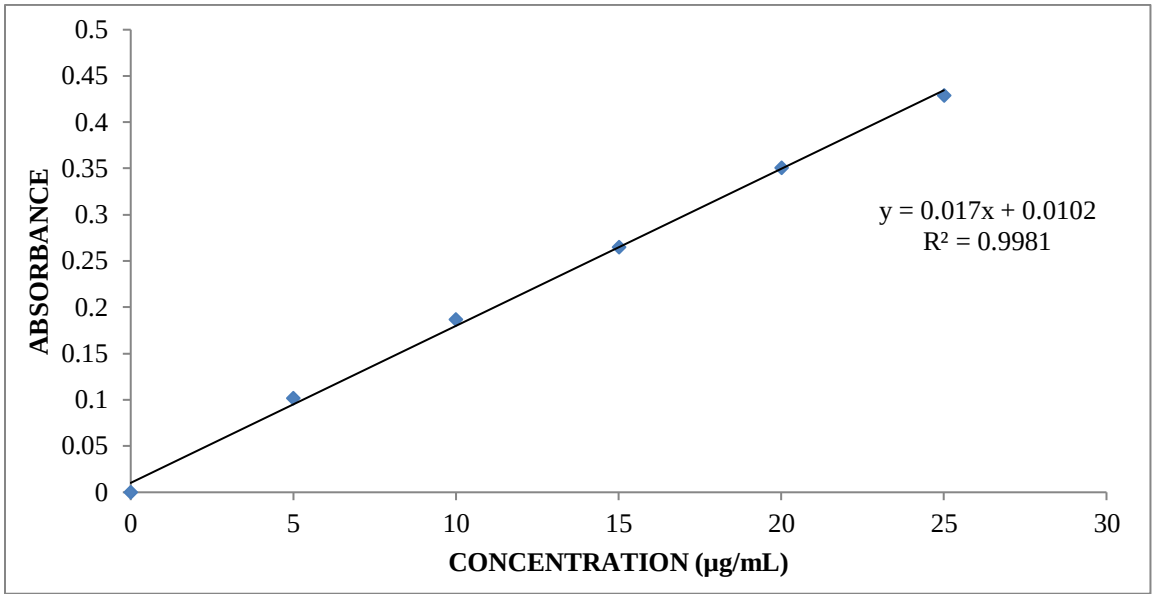

Fig 2: Standard graph of Perindopril in 0.1N HCL

Standard graph of Perindopril was plotted as per the procedure in experimental method and its linearity is shown in Table 2 and Fig 2. The standard graph of Perindopril showed good linearity with R^2 of 0.998, which indicates that it obeys "Beer- Lamberts" law.

Preformulation parameters of powder blend

Table 3: 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	25.56±0.3	0.57±0.01	0.61±0.01	10.11±0.8	1.13±0.02
F2	24.67±0.3	0.53±0.01	0.68±0.03	10.23±0.5	1.12±0.03
F3	25.56±0.2	0.52±0.06	0.64±0.03	10.34±1.0	1.14±0.06
F4	23.30±0.1	0.50±0.21	0.66±0.12	10.23±0.5	1.12±0.06
F5	22.56±0.1	0.65±0.02	0.59±0.02	11.23±0.8	1.11±0.05
F6	23.89±0.2	0.50±0.04	0.68±0.04	11.34±0.6	1.14±0.03
F7	26.54±0.1	0.59±0.04	0.64±0.05	10.12±0.7	1.13±0.09
F8	23.67±0.3	0.58±0.12	0.58±0.04	10.23±1.0	1.11±0.07
F9	24.34±0.4	0.56±0.02	0.54±0.01	10.23±0.8	1.13±0.02

Tablet 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 0.50±0.04 to 0.65±0.02 (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 0.54±0.01 to 0.54±0.01 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 10.34 which shows that the powder has good flow properties. All the formulations has shown the hausners ratio ranging between 1.11 to 1.14 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.

Table 4. *In vitro* quality control parameters

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag time (sec)	Total Floating Time (Hrs)
F1	96.13	4.3	0.34	2.15	96.34	52	6
F2	95.37	5.2	0.46	2.69	99.15	46	7
F3	98.01	4.6	0.29	2.81	98.24	35	9
F4	99.75	4.9	0.62	2.79	99.62	48	5
F5	97.54	5.1	0.72	2.56	97.49	30	6
F6	100.07	4.2	0.69	2.11	99.35	25	10
F7	100.01	5.0	0.28	2.29	98.12	46	8
F8	98.69	5.1	0.47	2.50	99.9	41	8
F9	100.01	4.6	0.52	1.74	97.84	35	7

All the parameters for SR layer such as weight variation, friability, hardness, thickness, drug content were found to be within limits.

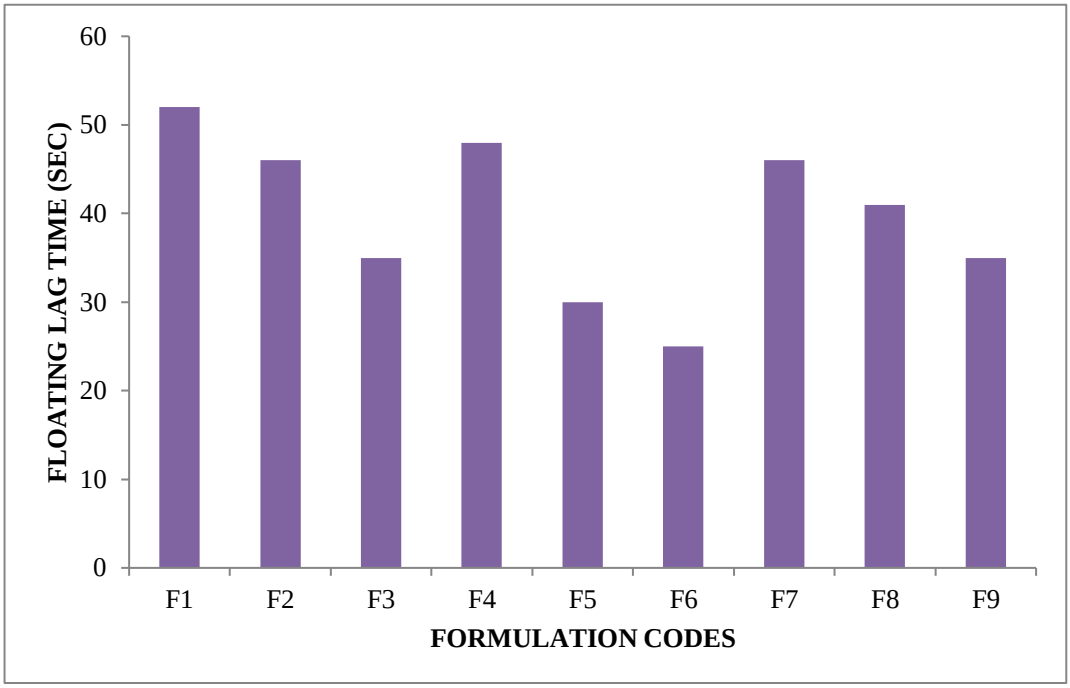

Figure 3: Floating lag time (sec)

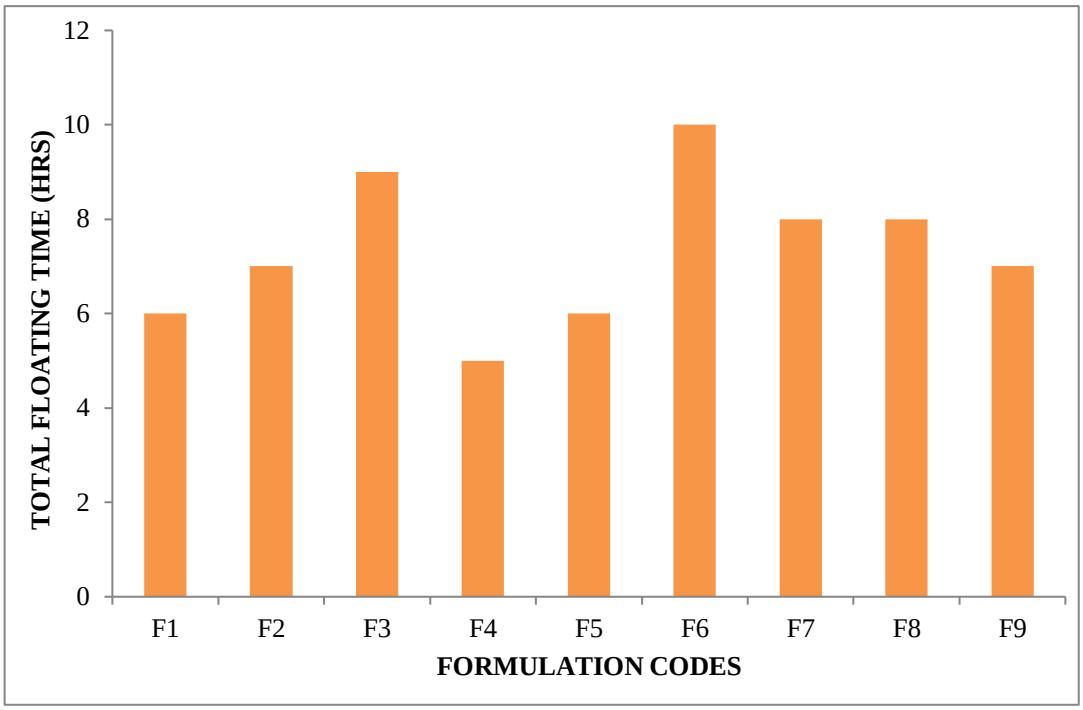

Figure 4: Total Floating Time (Hrs)

In vitro drug release studies

Table no 5: Dissolution data of Floating tablets

Time (H)	% OF DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	30.02	26.98	17.23	42.97	21.82	18.31	13.02	11.49	9.07
1	42.21	31.44	26.38	50.65	36.31	22.38	18.82	15.21	13.31
2	50.80	45.23	34.79	68.16	41.23	31.43	23.05	20.07	21.03
3	58.19	51.62	41.88	70.98	46.96	36.86	30.69	27.17	24.12
4	64.05	58.90	48.54	78.29	54.35	41.75	38.33	34.56	31.13
5	72.10	66.49	56.17	82.73	62.02	46.46	44.26	40.58	39.09
6	89.93	74.36	65.62	91.22	70.75	51.13	56.85	48.27	48.17
7	92.51	80.22	72.93	98.49	78.13	58.16	62.59	58.68	55.24
8	98.78	86.19	76.87		86.84	65.77	68.96	65.37	64.36
9		91.76	80.26		98.19	70.85	73.27	72.77	68.81
10		98.21	86.15			83.49	78.59	77.42	75.63
11			90.02			96.88	85.14	82.12	79.43
12			97.15			100.05	95.89	89.28	87.19

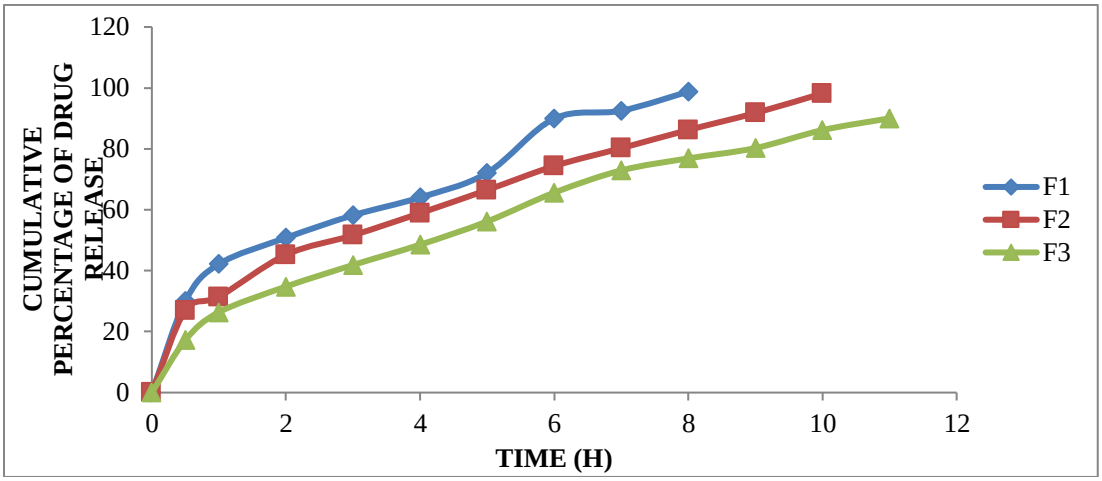

Fig 5: Dissolution data of Perindopril Floating tablets containing Carbapol 934

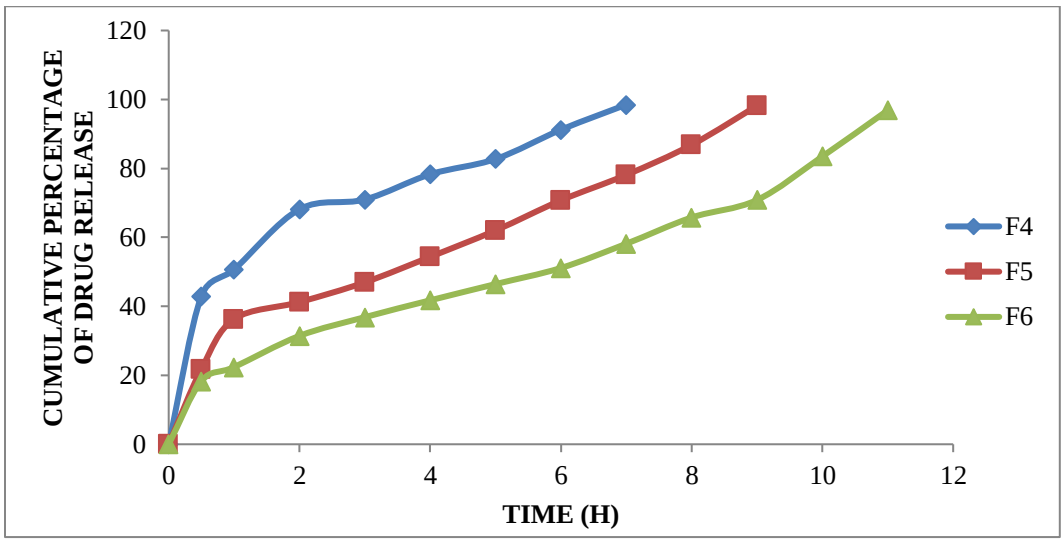

Fig: 6 Dissolution data of Perindopril Floating tablets containing HPMC K 100

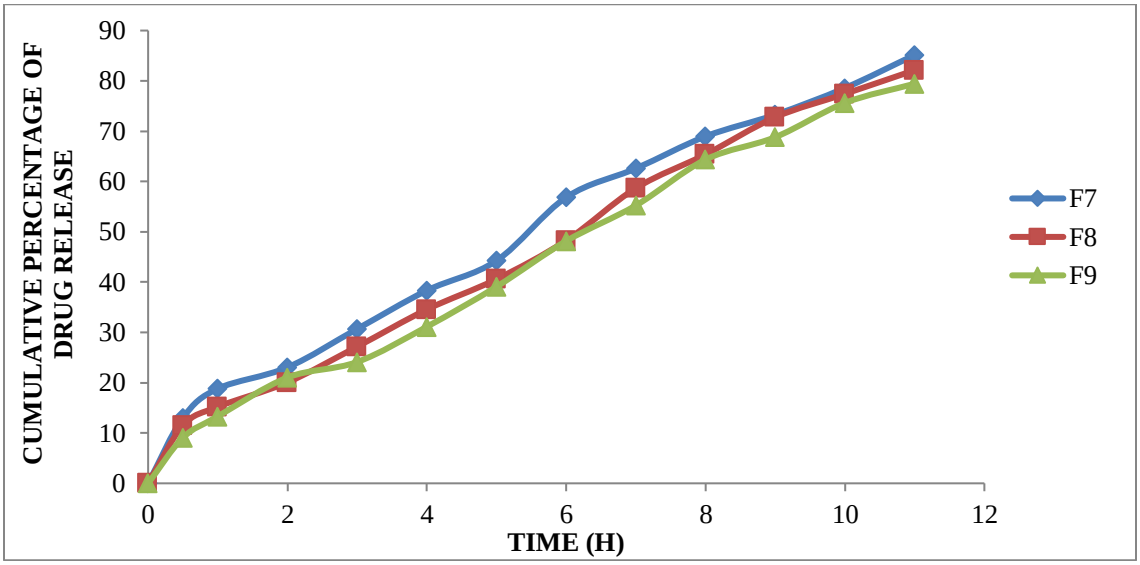

Fig: 7 Dissolution data of Perindopril Floating tablets containing Eudragit RSPO

From the dissolution data it was evident that the formulations prepared with Carbapol 934 as polymer were did not retarded the drug release 12 hours.
Whereas the formulations prepared with HPMC K 100 were retarded the drug release up to 12 hours in the all ratios. In higher concentrations the polymer was retard the drug release.

Whereas the formulations prepared with Eudragit RSPO were retarded the drug release in the concentration of 7 mg (F7 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 95.89 % in 12 hours with good retardation.

Hence from the above dissolution data it was concluded that F6 formulation was considered as optimized formulation because good drug release (100.05%) in 12 hours.

Application of release rate kinetics to Dissolution data for optimised formulation

Table no 6: 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	Qt 1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
18.31	0.5	0.707	1.263	-0.301	1.912	36.620	0.0546	-0.737	81.69	4.642	4.339	0.303
22.38	1	1.000	1.350	0.000	1.890	22.380	0.0447	-0.650	77.62	4.642	4.266	0.376
31.43	2	1.414	1.497	0.301	1.836	15.715	0.0318	-0.503	68.57	4.642	4.093	0.549
36.86	3	1.732	1.567	0.477	1.800	12.287	0.0271	-0.433	63.14	4.642	3.982	0.660
41.75	4	2.000	1.621	0.602	1.765	10.438	0.0240	-0.379	58.25	4.642	3.876	0.765
46.46	5	2.236	1.667	0.699	1.729	9.292	0.0215	-0.333	53.54	4.642	3.769	0.873
51.13	6	2.449	1.709	0.778	1.689	8.522	0.0196	-0.291	48.87	4.642	3.656	0.986
58.16	7	2.646	1.765	0.845	1.622	8.309	0.0172	-0.235	41.84	4.642	3.472	1.170
65.77	8	2.828	1.818	0.903	1.534	8.221	0.0152	-0.182	34.23	4.642	3.247	1.395
70.85	9	3.000	1.850	0.954	1.465	7.872	0.0141	-0.150	29.15	4.642	3.078	1.564

83.49	10	3.162	1.922	1.000	1.218	8.349	0.0120	-0.078	16.51	4.642	2.546	2.095
96.88	11	3.317	1.986	1.041	0.494	8.807	0.0103	-0.014	3.12	4.642	1.461	3.180
100.05	12	3.464	2.000	1.079		8.338	0.0100	0.000	-0.05	4.642	-0.368	5.010

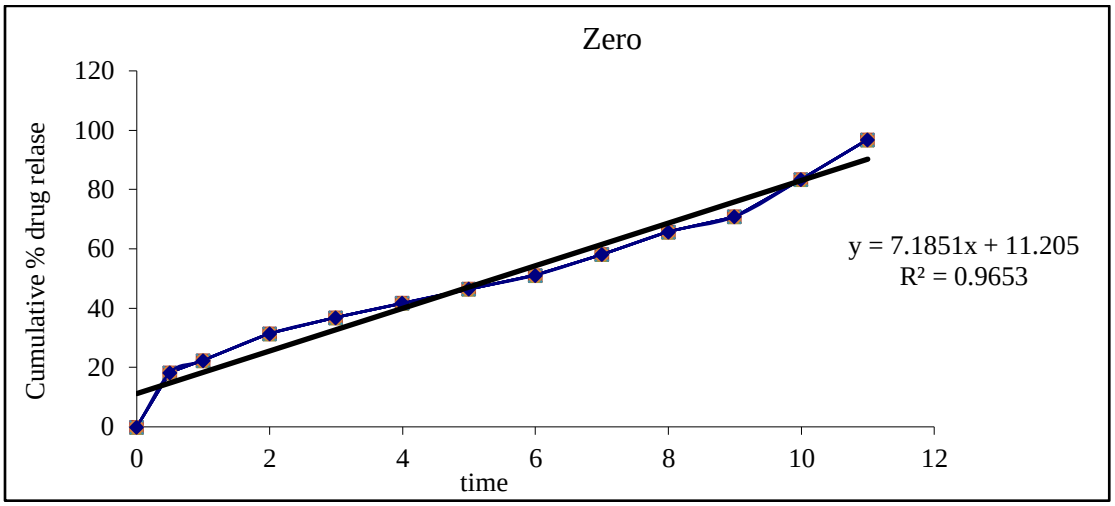

Fig no 8 : Zero order release kinetics

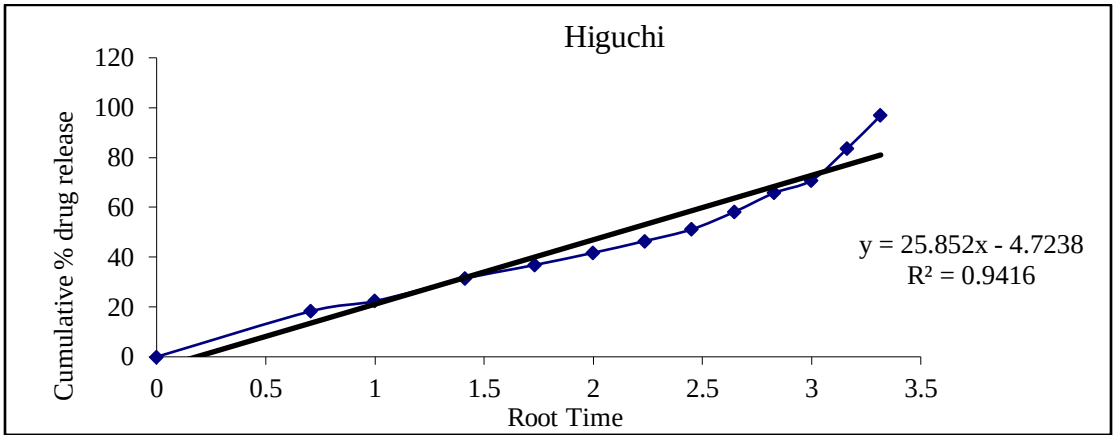

Fig no 9: Higuchi release kinetics

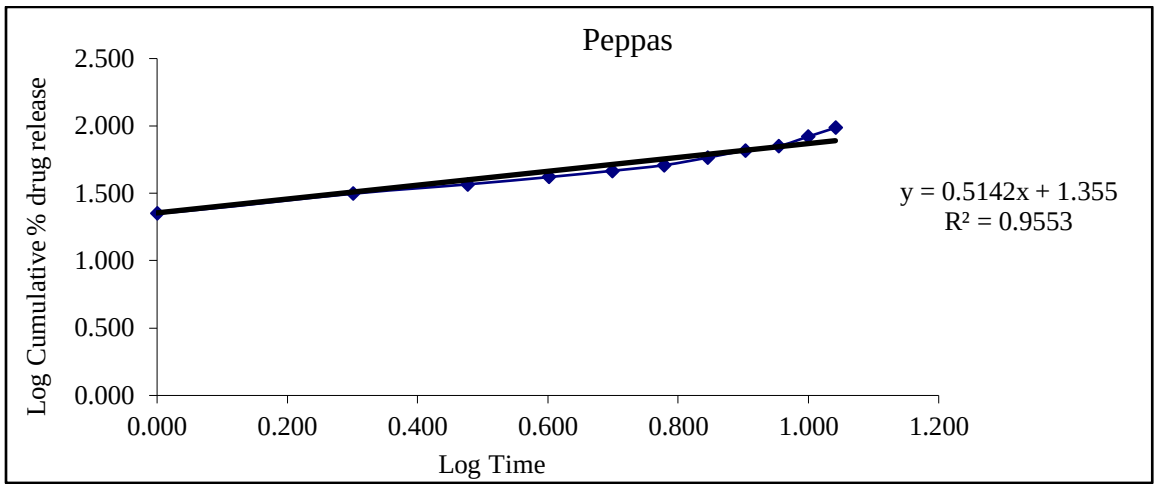

Fig 10: Kors mayer peppas release kinetics

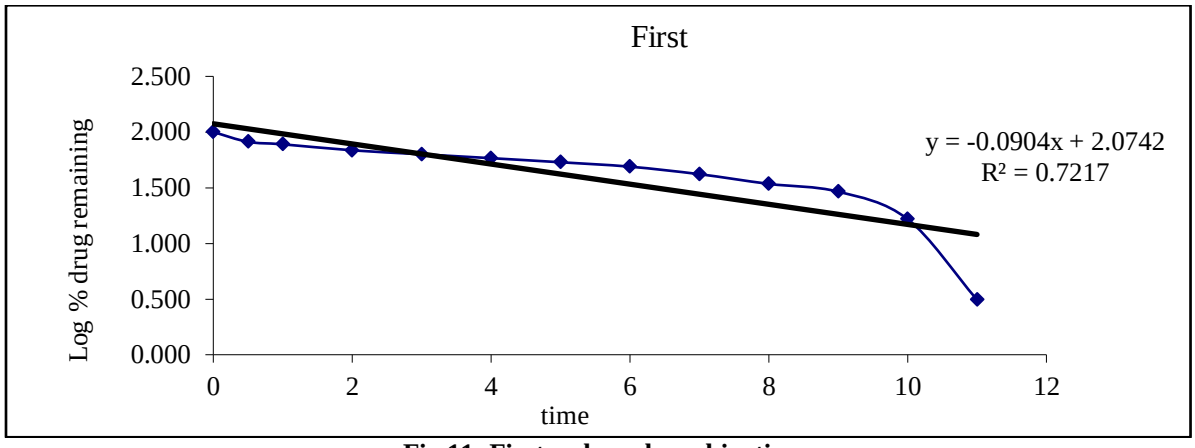

Fig 11: First order release kinetics

Optimised formulation F6 was kept for release kinetic studies. From the above graphs it was evident that the formulation F6 was followed **Zero order release kinetics** mechanism.

Drug – Excipient compatibility studies

Fourier Transform-Infrared Spectroscopy

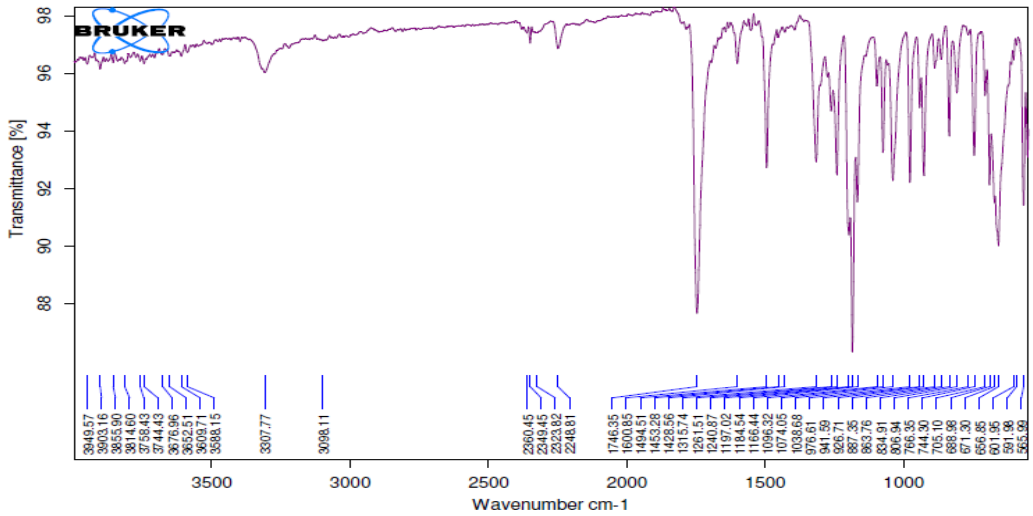

Figure 12: FTIR Spectrum of pure drug

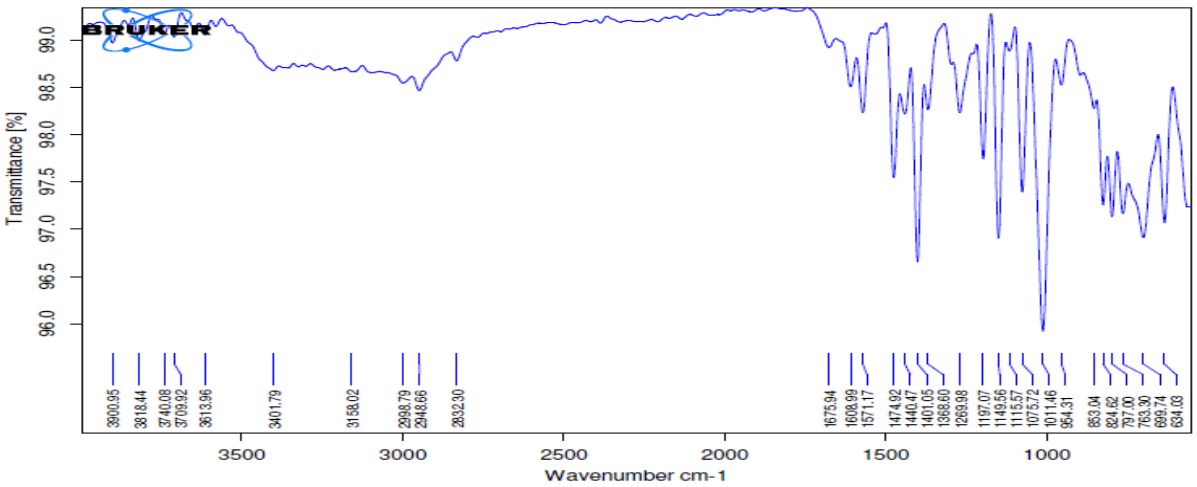

Fig 13: FTIR Spectrum of optimised formulation

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 is 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.

CONCLUSION

In the present study gastro-retentive floating tablets of Perindopril were successfully prepared by direct compression method using a number of ingredients like Carbapol 934, HPMC K 100, Eudragit RSPO, Sodium Bicarbonate, Talc and Magnesium stearate. Standard graph was given that regression analysis R^2 value was 0.998 in 0.1 N HCl. FTIR results were shown good compatibility between drug and excipients. For each formulation blend of the drug and excipients were prepared and evaluated, the tablets were compressed by direct compression method. Pre-compression parameters were tested for each and every formulation batch and were found to be satisfactory. *In-vitro* drug release studies were carried out for all prepared formulation and from that concluded F6 formulation has shown good results finally concluded release kinetics to optimised formulation (F6) has followed Zero order release kinetics.

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