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Effect of Hydrophillic Polymers on Gastro Retentive Floating Matrix Tablets of Lisinopril

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ABSTRACT

In the present research work gastro retentive floating matrix formulation of Lisinopril by using various hydrophilic polymers were developed. Then the formulation was developed by using different concentrations of polymers of HPMC K 4 M, HPMC K 15 M and HPMC K 100M as polymeric substances. The formulation blend was subjected to various preformulation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations the formulation F5 with HPMC K 15 M was retarded the drug release (96.73 %) desired time period. The dissolution data of optimized formulation (F5) was subjected to release kinetics; from the release kinetics data it was evident that the formulation followed Zero order release kinetics (R^2 =0.996).

Keywords: Lisinopril, Floating tablets. HPMC K 4 M, HPMC K 15 M, HPMC K 100 M, Release Kinetics.

INTRODUCTION

Oral delivery of drugs is the most preferable route of drug delivery. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient compliance and flexibility in formulation and cost effective manufacturing process [1]. Many of the drug delivery systems, available in the market are oral drug delivery type systems Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption [2].

Tablets are the most conventional and economic pharmaceutical formulations prepared to release the medicament after oral administration. Time and cost effectiveness make tablets still the favored dosage forms. The performance of tablet depends on its matrix and surface properties, which govern the mechanical and chemical properties of tablet. Conventional release tablets result in relatively increased number of dosages. These conventional tablets may show more fluctuations in plasma drug concentration. To avoid the fast sub-therapeutics level of the drug another dose is usually given for treating chronic diseased conditions [3].

To overcome the limitation of conventional tablets, development of various modified release drug products is gaining more attention to control the drug release [4]. Modified release products use polymers to alter the rate of drug release under controlled pH conditions of gastrointestinal tract (G.I.T). The term controlled-release was originally used to depict various extended release formulations such as prolonged action, sustained-release, slow-release, long-action and programmed delivery [5]. The basic rational of controlled or sustained release formulation is to control drug at target site, avoiding the frequent dosing and improve efficacy effect of a drugs by altering its pharmacokinetics and pharmacodynamic profile [6].

However, such controlled delivery systems extend limited advantages for bioactives having narrow therapeutic window. Various drugs such as gliclazide and pioglitazone are absorbed from duodenum and jejunum [7]. However, limited absorption may be possible at these sites due to the quick passage of dosage form (about 1-2 h) [8-11]. To meliorate the

oral availability of these therapeutics, the retention time of the delivery system need to be extended in the stomach, so that the drug will be available in the solution form when it reached to the area from where its maximum absorption is possible [12]. This can be successfully accomplished by developing gastroretentive controlled release carrier that can resist the grinding, crushing, contractions, and peristaltic movements and allow prolonged drug release [13-15]. Retention for prolonged period of time leads to improved oral bioavailability, and clinical efficacy, also reduces the number of dosage administration and improves patient compliance [16]. Hence, extended release drug delivery systems with gastric retention are recommended as potential delivery systems for effective drug delivery [17].

Advantages of Floating tablets

- Floating drug delivery offers several applications for drugs having poor Bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract.
- It retains the dosage forms at the site of absorption and thus enhances the Bioavailability.
- Sustained Drug Delivery
- Site Specific Drug Delivery
- Improved plasma levels [18].

Disadvantages

- High variability in gastric emptying time due to variations in emptying process.
- Unpredictable bioavailability.
- Floating system is not feasible for those drugs that have solubility or stability problem in gastric fluids.
- The dosage form should be administered with a minimum of glass full of water.
- The drugs, which are absorbed throughout gastro-intestinal tract, which under go first-pass metabolism (Nifedipine, Propranolol etc.) are not desirable candidate.
- Some drugs present in the floating system causes irritation to gastric mucosa [19].

Absorption of Lisinopril is slow, variably, and incomplete (~30%) after oral administration. To overcome this limitation of Lisinopril, the present study was designed to develop floating gastroretentive tablets by wet granulation technique. Lisinopril is lysine derivative of enalapril. It is competitive inhibitor of angiotensin converting enzyme which inhibits conversion of angiotensin I into angiotensin II which is potent vasoconstrictor. Angiotensin II causes the release of aldosterone from adrenal cortex. Lisinopril is used primarily in treatment of hypertension, congestive heart failure, and heart attacks, and in preventing renal and retinal complications of diabetes. Its indications, contraindications, and side effects are as those for all ACE inhibitors [20].

The main aim of the Research work is to study the effect of polymers on drug release of gastro retentive floating tablets of Lisinopril using various hydrophilic polymers and Sodium Bicarbonate as effervescent agent. The main objectives include optimizing the concentration and viscosity of various hydrophilic polymer of HPMC. To formulate and perform the various *in vitro* evaluation test parameters for Gastro retentive floating tablets.

METHODOLOGY

The entire research work was followed the plan of methodology [21]

1. Literature survey
2. Selection and procurement of suitable drug candidate and excipients.
3. Preparation of standard graph of Lisinopril.
4. Preformulation studies
   - Drug and excipient compatibility studies using FTIR.
5. Formulation of floating tablets of Lisinopril
   - Optimization of sodium bicarbonate
   - Formulation development of Lisinopril floating tablets using various polymers
6. Evaluation parameters
   - Pre compression parameters
   - Angle of repose
   - Bulk density
   - Tapped density
   - Carr's Index
   - Hausners ratio
   - Post compression parameters
   - Thickness

- Hardness
- Friability
- Weight variation test
- Drug content of Lisinopril
- *In-vitro* buoyancy studies
- *In-vitro* dissolution studies

7. Selection of optimized formulation.
8. Application of release kinetics on optimized formula.

Table 1: Formulation composition for floating tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lisinopril (mg)	20	20	20	20	20	20	20	20	20
HPMC K 4 M	20	40	60	-	-	-	-	-	-
HPMC K 15 M	-	-	-	20	40	60	-	-	-
HPMC K 100 M	-	-	-	-	-	-	20	40	60
$NaHCO_3$	40	40	40	40	40	40	40	40	40
Mag. Stearate	4	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4	4
MCC pH102	QS	QS	QS	QS	QS	QS	QS	QS	QS
Total weight	200	200	200	200	200	200	200	200	200

HPMC: Hydroxy Propyl Methyl Cellulose **MCC:** Micro Crystalline Cellulose
Mag. Stearate: Magnesium stearate, **$NaHCO_3$:** Sodium bicarbonate

RESULTS AND DISCUSSION

The present study was aimed to developing gastro retentive floating tablets of Lisinopril using natural polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Analytical Method
Graph of Lisinopril was taken in Simulated Gastric fluid at 215 nm.

Drug – Excipients compatibility studies
Fourier Transform-Infrared Spectroscopy:

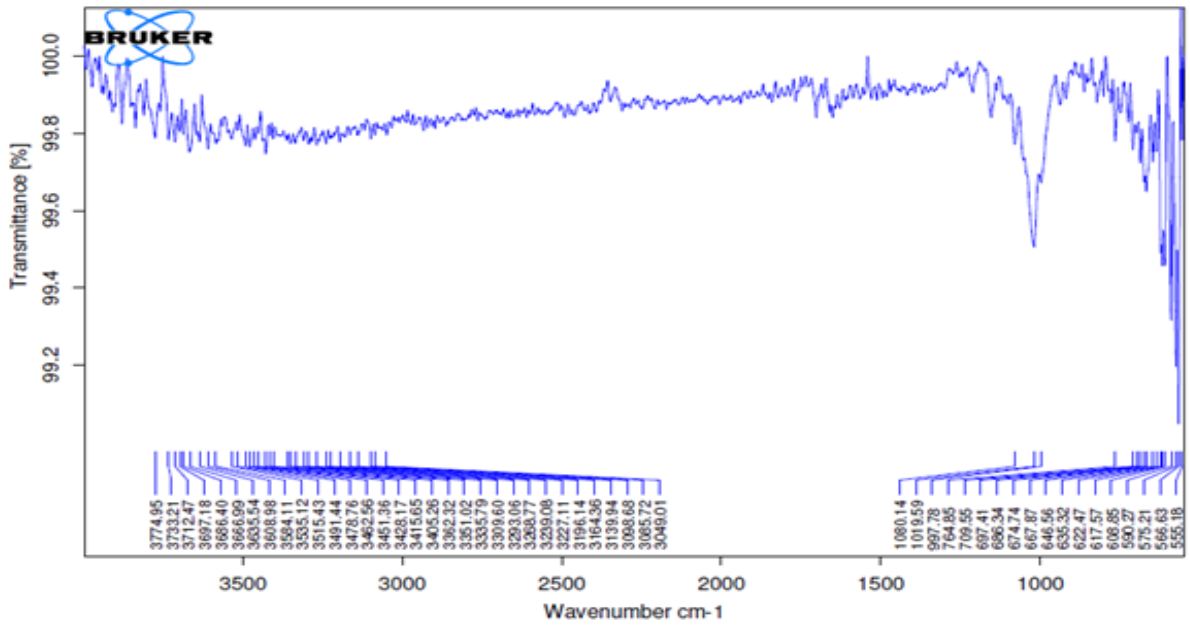

Figure 1: FT-TR Spectrum of Lisinopril pure drug.

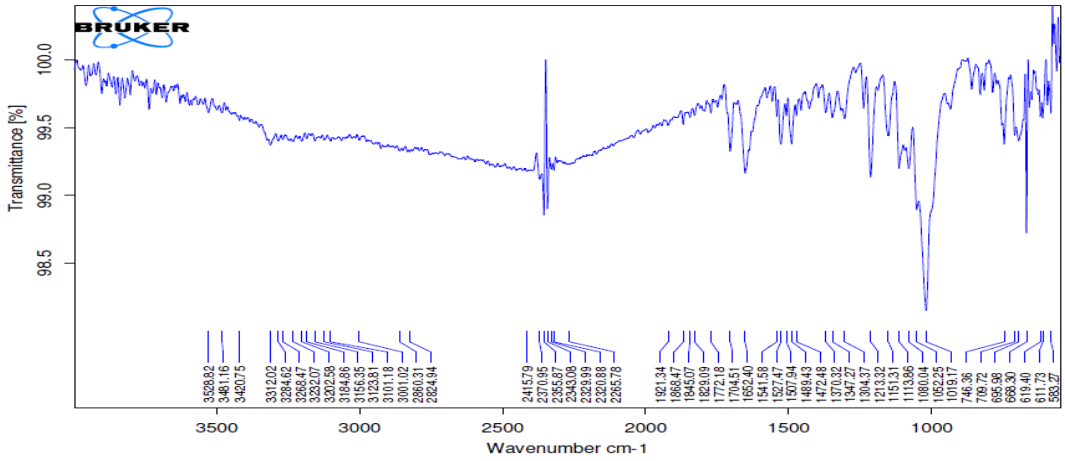

Figure 2: FT-IR Spectrum of Optimized Formulation of Lisinopril tablets Preformulation parameters of powder blend

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	24.12 ± 0.86	0.36 ± 0.01	0.43 ± 0.07	16.27±0.09	1.19±0.04
F2	21.63 ± 0.27	0.34 ± 0.01	0.41 ± 0.01	17.07±0.07	1.20±0.08
F3	25.54 ± 0.91	0.32 ± 0.02	0.40 ± 0.06	20.00±0.06	1.25±0.02
F4	22.36 ± 0.54	0.35 ± 0.06	0.42 ± 0.08	16.66±0.06	1.20±0.07
F5	28.63 ± 0.23	0.37 ± 0.04	0.46 ± 0.01	19.56±0.05	1.24±0.03
F6	24.17 ± 0.14	0.36 ± 0.06	0.45 ± 0.02	20.01±0.07	1.25±0.06
F7	23.69 ± 0.39	0.39 ± 0.05	0.48 ± 0.04	18.75±0.04	1.23±0.07
F8	26.18 ± 0.61	0.37 ± 0.03	0.46 ± 0.03	19.56±0.02	1.24±0.03
F9	25.05 ± 0.81	0.31 ± 0.02	0.39 ± 0.01	20.51±0.08	1.25±0.06

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 0.31 ± 0.02 to 0.39 ± 0.05 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.39 ± 0.01 to 0.48 ± 0.04 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging from 16.27±0.09 to 20.51±0.08 which show that the powder has good flow properties. All the formulations have shown the Hausner's ratio ranging from 1.19±0.04 to 1.25±0.06 indicating the powder has good flow properties.

Optimization of sodium bicarbonate concentration:
Three formulations were prepared with varying concentrations of sodium bicarbonate. The formulation containing sodium bicarbonate in 40 mg concentration showed less floating lag time of 1 min and the tablet was in floating condition for more than 12 hours.

Post compression Parameters for tablets:
Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the tablets. All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

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

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Friability (% loss)	Thickness (mm)	Drug content (%)	Floating lag time (min)	Duration of floating time
F1	202.6 ± 0.86	5.6 ± 0.01	0.61 ± 0.05	4.5 ± 0.02	95.14 ± 0.14	0.50 ±0.01	<5 hr

F2	200.3 ± 0.91	5.1 ± 0.02	0.39 ± 0.08	4.5 ± 0.01	97.12 ± 0.16	1.10±0.02	8 hr
F3	199.4 ± 0.63	5.3 ± 0.03	0.51 ± 0.12	4.4 ± 0.03	96.93 ± 0.19	1.40 ±0.05	> 7 hr
F4	202.5 ± 0.48	5.0 ± 0.02	0.48 ± 0.09	4.5 ± 0.02	98.14 ± 0.24	0.30 ±0.04	9 hr
F5	197.8 ± 0.37	5.6 ± 0.01	0.43 ± 0.10	4.4 ± 0.02	97.24 ± 0.23	0.45±0.06	12 hr
F6	200.1 ± 1.01	5.8 ± 0.02	0.71 ± 0.15	4.5 ± 0.01	98.36 ± 0.48	0.56± 0.07	> 12 hr
F7	197.6 ± 0.94	5.8 ± 0.03	0.29 ± 0.09	4.4 ± 0.01	98.28 ± 0.36	0.37±0.06	12 hr
F8	196.3 ± 0.77	5.6 ± 0.01	0.66 ± 0.12	4.4 ± 0.02	98.56 ± 0.21	0.39±0.01	> 12 hr
F9	201.8 ± 1.91	5.7 ± 0.02	0.74 ± 0.13	4.5 ± 0.01	97.21 ± 0.72	0.34±0.07	> 12 hr

Weight variation and thickness: All the formulations were evaluated for uniformity of weight using electronic weighing balance and the results are shown in table 4. The average tablet weight of all the formulations was found to be between 196.3 ± 0.77 to 202.6 ± 0.86**.** The maximum allowed percentage weight variation for tablets weighing <250 mg is 7.5% and no formulations are not exceeding this limit. Thus all the formulations were found to comply with the standards given in I.P. And thickness of all the formulations was also complying with the standards that were found to be between 4.4 ± 0.01 to 4.5 ± 0.02.

Hardness and friability: All the formulations were evaluated for their hardness, using monsanto hardness tester and the results are shown in table 4. The average hardness for all the formulations was found to be from 5.0 ± 0.02 to 5.8 ± 0.03 Kg/cm^2 which were found to be acceptable.

Friability was determined to estimate the ability of the tablets to withstand the abrasion during packing, handling and transporting. All the formulations were evaluated for their percentage friability using Roche friabilator and the results were shown in table 4. The average percentage friability for all the formulations was between 0.29 ± 0.09 and 0.74 ± 0.13, which was found to be within the limit.

Drug content: All the formulations were evaluated for drug content according to the procedure described in methodology section and the results were shown in table 4. The drug content Values for all the formulations were found to be in the range of **(**95.14 ± 0.14 to 98.56 ± 0.21**).** According to IP standards the tablets must contain not less than 95% and not more than 105% of the stated amount of the drug. Thus, all the formulations comply with the standards given in IP.

***In vitro* buoyancy studies:** All formulations were examined for buoyancy studies, in that to determine the floating lag time and duration of floating time. The floating lag time of most of the formulations were showed within 1 minute only. But duration of floating time was difference, it dependence on the concentration of polymer and type of polymer. Among all the formulation F5 to F9 were showed 12 hours or more than 12 hours

***In-Vitro* Drug Release Studies**

Table 4: Dissolution Data of Lisinopril Tablets Prepared With HPMC K 4 M

Time (hr)	**Cumulative Percent Drug Released** (n=3 ± SD)		
	F1	**F2**	**F3**
0	0	0	0
0.5	14.66	12.34	11.42
1	26.38	20.08	18.67
2	39.61	36.92	32.41
3	51.63	43.76	40.06
4	69.07	58.16	49.77
5	82.63	67.44	58.46
6	96.55	74.28	70.16
7	-	87.09	83.855
8	-	98.57	94.55
9	-	-	94.55
10	-	-	-
11	-	-	-
12	-	-	-

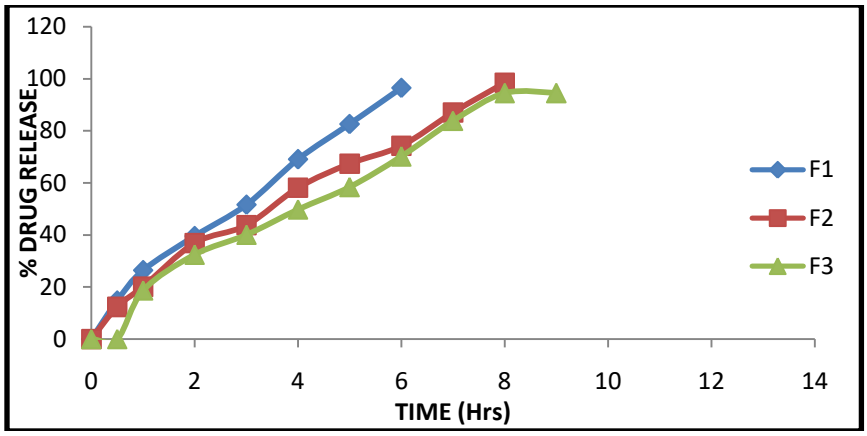

Figure 3: Dissolution profile of Lisinopril floating tablets (F1, F2, F3 formulations).

Table 5: Dissolution Data of Lisinopril Tablets Prepared With HPMC K 15 M

Time (hr)	Cumulative Percent Drug Released (n=3±sd)		
	F4	F5	F6
0	0	0	0
0.5	8.45	6.32	3.61
1	13.21	10.24	8.14
2	21.56	16.43	12.87
3	36.57	21.67	20.74
4	49.36	29.18	26.39
5	62.25	38.69	32.98
6	73.96	45.71	39.74
7	84.26	52.33	46.19
8	99.734	60.09	51.38
9	-	70.18	58.16
10	-	79.67	65.73
11	-	84.13	71.58
12	-	96.73	76.32

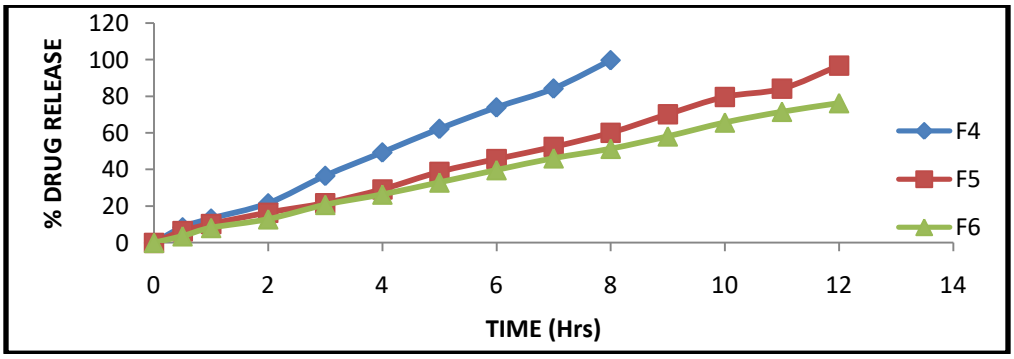

Figure 4: Dissolution profile of Lisinopril floating tablets (F4, F5, F6 formulations)

Table 6: Dissolution Data of Lisinopril tablets prepared with HPMC K 100 M

Time (hr)	Cumulative Percent Drug Released (n=3±sd)		
	F7	F8	F9
0	0	0	0
0.5	2.85	2.01	1.16

1	8.26	6.59	3.54
2	10.35	11.34	8.63
3	17.58	15.94	13.54
4	21.41	20.18	19.22
5	29.07	26.34	25.31
6	36.73	32.98	30.57
7	40.56	41.36	38.46
8	48.22	50.83	43.12
9	65.59	59.61	48.34
10	71.63	66.14	55.69
11	79.37	74.31	62.17
12	90.14	86.19	69.13

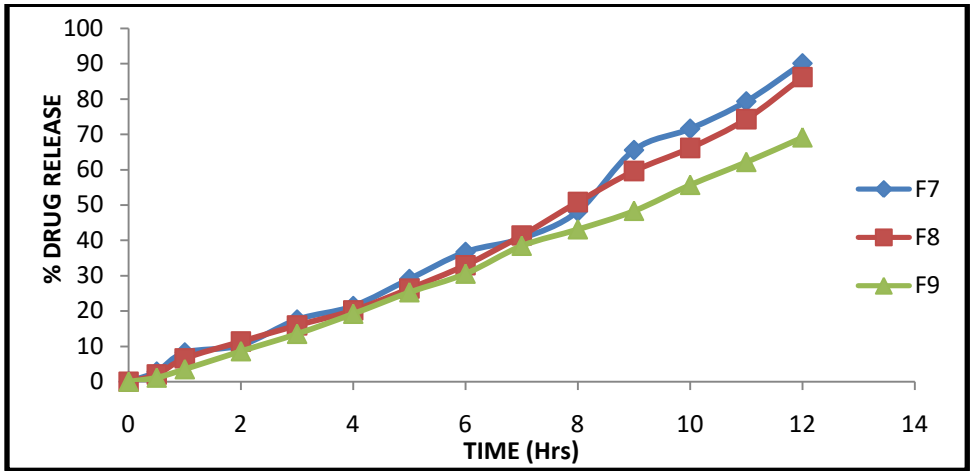

Figure 5: Dissolution profile of Lisinopril floating tablets (F7, F8, F9 formulations)

From the dissolution data it was evident that the formulations prepared with HPMC K 4 M was unable to retard the drug release up to desired time period. The formulations prepared with HPMC K 15 M also unable to retard the drug release at lower concentration of polymer whenever increase the concentration of HPMC K 15 M in the formulation (F5) it was showed maximum drug release at 12 hours. The drug release of formulations prepared with HPMC K 100 M at retarded the drug release more than 12 hours. Among all the formulation, F5 formulation was considered as optimized formulation.

Application of Release Rate Kinetics to Dissolution Data

Stated 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.

Table 7: Release kinetics data for optimised formulation

Cumulative (%) Release (Q)	Time (T)	Root (T)	Log (%) Release	Log (T)	Log (%) Remain
0	0	0			2.000
6.32	0.5	0.707	0.801	-0.301	1.972
10.24	1	1.000	1.010	0.000	1.953
16.43	2	1.414	1.216	0.301	1.922
21.67	3	1.732	1.336	0.477	1.894
29.18	4	2.000	1.465	0.602	1.850
38.69	5	2.236	1.588	0.699	1.788
45.71	6	2.449	1.660	0.778	1.735

52.33	7	2.646	1.719	0.845	1.678
60.09	8	2.828	1.779	0.903	1.601
70.18	9	3.000	1.846	0.954	1.475
79.67	10	3.162	1.901	1.000	1.308
84.13	11	3.317	1.925	1.041	1.201
96.73	12	3.464	1.986	1.079	0.515

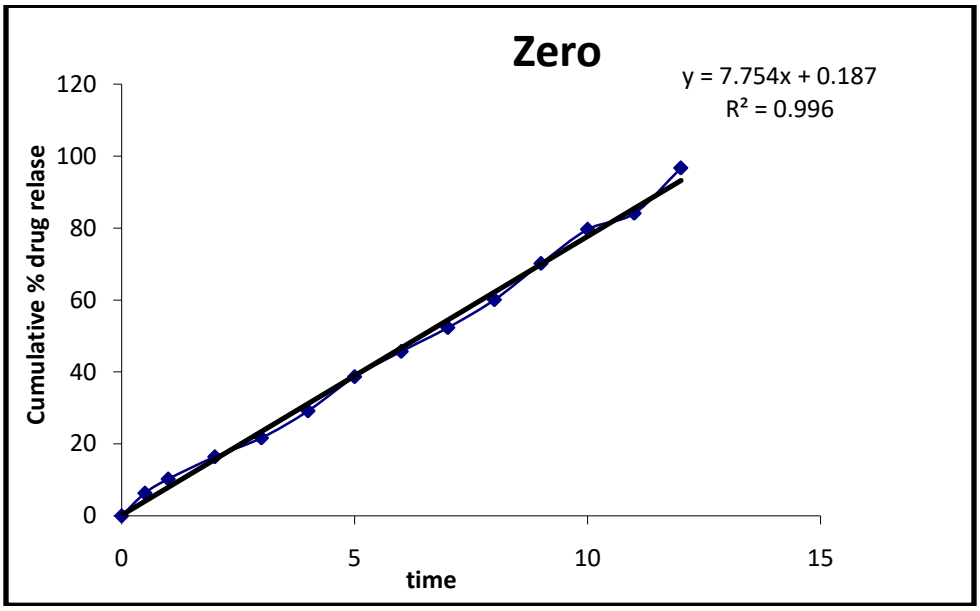

Figure 6 : Zero order release kinetics graph

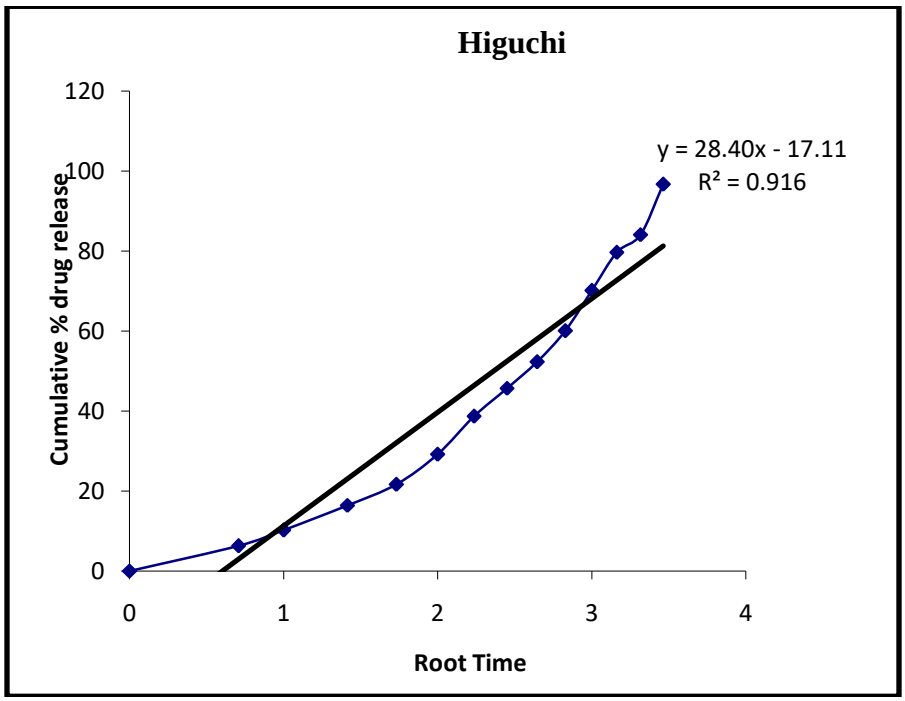

Figure 7 : Higuchi release kinetics graph

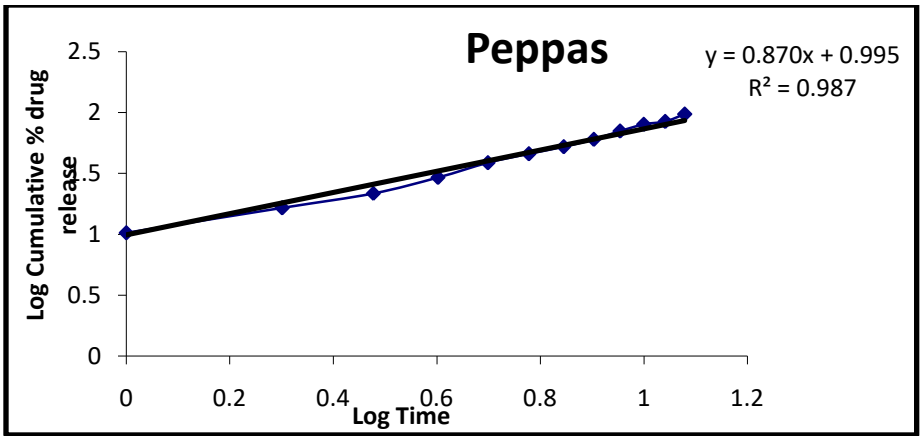

Figure 8: Kars mayer peppas graph

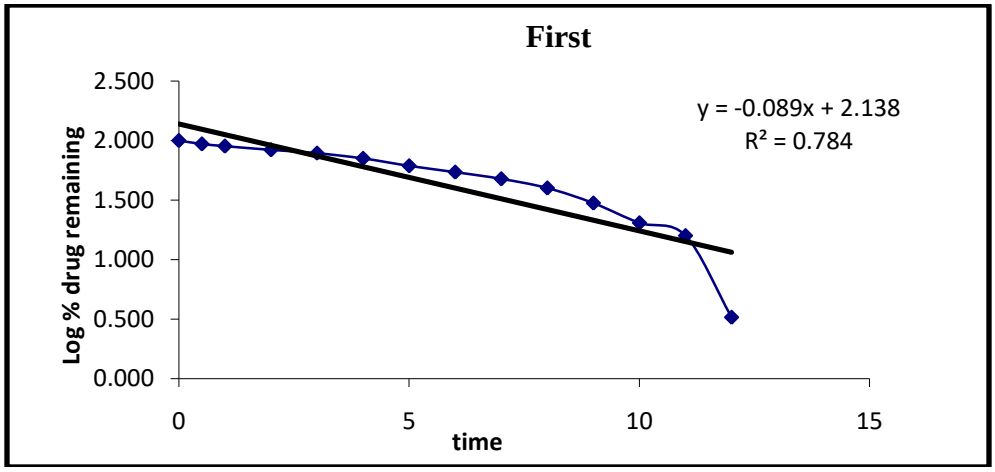

Figure 9: First order release kinetics graph

From the above graphs it was evident that the formulation F5 was followed Zero order release kinetics.

CONCLUSION

The present research work carried out on gastro retentive floating tablets of Lisinopril by using different concentrations of Hydroxy Propyl Methyl Cellulose (HPMC K4M, K 15M, K100M) as drug release retarding hydrophilic polymer in different viscosity grades.. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Gas generating agent sodium bicarbonate concentration was optimized. The formulation blend was subjected to various preformualation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. The present study concludes that gastro retentive floating tablets of Lisinopril prepared using HPMC K 4 M, HPMC K 15 M and HPMC K 100 M as retarding polymers. Among all the formulations the formulation F5 with HPMC K 15 M was retarded the drug release (96.73 %) desired time period of 12 hours and that the formulation F5 was followed Zero order release kinetics (R^2 =0.996). Present study concludes that there is an effect of hydrophilic polymer in different viscosity grades and in different concentrations on gastro retentive floating tablets of Lisinopril.

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