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FORMULATION AND *INVITRO* EVALUATION OF EFFERVESCENT FLOATING TABLETS OF ATENOLOL

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Abstract:

Formulation and evaluation of floating tablets of Atenolol. In the present study the formulations were prepared by direct compression method using different proportions of HPMC K4M, HPMC K15M, and HPMC K100M as Swellable polymers. Sodium bicarbonate is used as buoyancy-imparting agent. The prepared formulations were evaluated for different parameters during its pre-compression and post-compression stages. The release characteristics of the formulations were studied in in-vitro conditions. The in-vitro dissolution study of formulation F8 was 99.41% within 12 h for good release and was fitted to kinetics of drug release for R^2 value of Higuchi release mechanism model is 0.964. As an extension of this work for formulation F8, bioavailability, pharmacokinetic, and in-vivo studies can be done in future to develop as suitable candidate for a novel drug delivery system.

Key words: *Atenolol, HPMC K4M, HPMC K15M, HPMC K100M and Floating Tablets.*

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INTRODUCTION:

The aim of drug delivery system is to afford a therapeutic amount of drug to the proper site in the body to attain promptly and then maintain desired drug concentration. The oral route is increasingly being used for the delivery of therapeutic agents because the low cost of the therapy and ease of administration lead to high levels of patient compliance. More than 50% of the drug delivery systems available in the market are oral drug delivery systems [1-4]. Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. The relatively brief gastric emptying time (GET) in humans which normally averages 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose. Sustained releases are dosage forms that provide medication over an extended period of time. Controlled release denotes that the system is able to provide some actual therapeutic control [5]. Controlled release (modified release) dosage forms are growing in popularity. These more sophisticated systems can be used as a means of altering the pharmacokinetic behavior of drugs in order to provide twice or once a day dosage. This is achieved by obtaining a zero-order release from the dosage form. Zero-order release includes drug release from the dosage form that is independent of the amount of drug in the delivery system.

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion , flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents, that delay gastric emptying. Oral controlled drug release dosage forms should not be developed unless the recommended dosage interval for the controlled release dosage form is longer than that for immediate release dosage form or unless significant clinical advantages for the controlled release dosage form can be justified like the decreased side effects resulting from a lower C max with the controlled release Form as compared to the immediate release or conventional dosage form. In vivo/in vitro evaluation of FDDS has been discussed by scientists to assess the efficiency and application of such systems. Several recent examples have been reported showing the efficiency of such systems for drugs with bioavailability problems.

The concept of floating tablets is mainly based on the matrix type drug delivery system such that the drug remains embedded in the matrix which after coming in contact with the gastric fluid swells up and the slow erosion of the drug without disintegration of the tablet takes place. Sometimes for generating a floating system we even need to add some effervescent or gas generating agent which will also ultimately reduce the density of the system and serve the goal of achieving a floating system. These systems have a particular advantage that they can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the GIT. These systems continuously release the drug before it reaches the absorption window, thus ensuring optimal bioavailability. Different approaches are currently used to prolong the gastric retention time, like hydro dynamically balanced systems, swelling and expanding systems, polymeric bio-adhesive systems, modified shape systems, high density systems and other delayed gastric emptying devices. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release .

MATERIALS AND METHODS:

Atenolol Procured from Aurobindo Laboratory, Hyderabad, Provided by SURA LABS, Dilsukhnagar, Hyderabad, HPMC K4M from Colorcon Asia Pvt. Limited, HPMC K15M from Colorcon Asia Pvt. Limited, HPMC K100M from Colorcon Asia Pvt. Limited, Lactose from Indchem International Ltd, Mumbai, India, NaHCO3 from S.D. Fine Chemicals, Mumbai, India, Magnesium stearate from S.D. Fine Chemicals, Mumbai, India, Talc from S.D. Fine Chemicals, Mumbai, India.

Analytical method development:

a) 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.

b) Preparation calibration curve:

10mg Atenolol 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 2, 4, 6, 8, 10µg

/ml of per ml of solution. The absorbance of the above dilutions was measured at 225 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.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$\tan\theta = h / r$ $\tan\theta$= Angle of repose

h = Height of the cone , r = Radius of the cone base

Table : Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density:

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment.10gm powder blend was sieved and introduced in toady 20ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated using the formula:

$$\text{Bulk Density} = M / V_o$$

Where, M = weight of sample

V_o = apparent volume of powder

Tapped density:

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than2% and then tapped volume, measured, to the nearest graduated unit. The tapped density was calculated, in gm perL, using the formula:

$$Tap = M / V$$

Where,Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

Measures of powder compressibility:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poor reflowing materials, there are frequently greater interparticle interactions, and greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

Carr's Index = [(tap - b) / tap] × 100

Where, b = Bulk Density

Tap= Tapped Density

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 8 mm punch.

Formulation of tablets:

Table : Formulation composition for Floating tablets

INGREDIENTS	FORMULATION CODE											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Atenolol	100	100	100	100	100	100	100	100	100	100	100	100
HPMC K4M	20	40	60	80	-	-	-	-	-	-	-	-
HPMC K15M	-	-	-	-	20	40	60	80	-	-	-	-
HPMC K100M	-	-	-	-	-	-	-	-	20	40	60	80
Lactose	112	92	72	52	112	92	72	52	112	92	72	52
$NaHCO_3$	10	10	10	10	10	10	10	10	10	10	10	10
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Total Weight	250	250	250	250	250	250	250	250	250	250	250	250

All the quantities were in mg

RESULT AND DISCUSSION:

Analytical Method

a. Determination of absorption maxima

The standard curve is based on the spectrophotometry. The maximum absorption was observed at 225 nm.

B. Calibration curve

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

Table no: Observations for graph of Atenolol in 0.1N HCl

Conc [µg/mL]	Abs
0	0
2	0.129
4	0.254
6	0.362
8	0.471
10	0.599

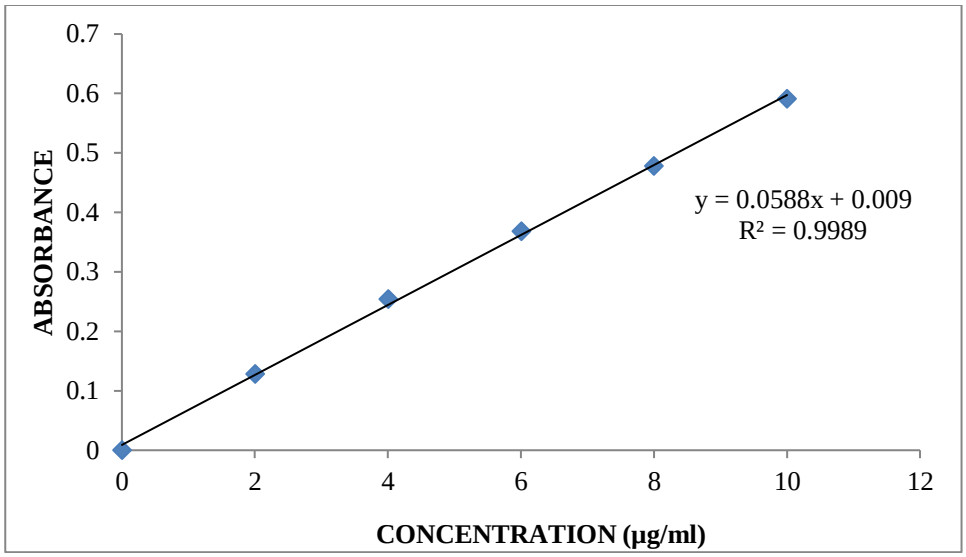

Fig: Standard graph of Atenolol in 0.1N HCL

Standard graph of Atenolol was plotted as per the procedure in experimental method and its linearity is shown in Table 8.1 and Fig 8.1. The standard graph of Atenolol showed good linearity with R^2 of 0.998, which indicates that it obeys "Beer- Lamberts" law.

Preformulation parameters of powder blend:

Table : 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	29.98±0.01	0.458±0.01	0.54±0.011	15.18±0.02	1.17±0.03
F2	23.75 ±0.01	0.446±0.05	0.539±0.09	17.25±0.07	1.20±0.02
F3	28.1±0.03	0.461±0.08	0.539±0.09	14.47±0.01	1.16±0.04
F4	26.57±0.05	0.405±0.06	0.5±0.04	19±0.02	1.23±0.03
F5	28.07±0.02	0.418±0.01	0.505±0.02	17.22±0.08	1.20±0.01
F6	29.73±0.02	0.449±0.05	0.518±0.06	13.32±0.02	1.15±0.03
F7	30.96±0.06	0.405±0.05	0.468±0.06	13.46±0.01	1.15±0.04
F8	32.01±0.04	0.409±0.04	0.478±0.07	14.43±0.02	1.16±0.02
F9	28.01± 0.04	0.469±0.04	0.525±0.08	10.66±0.02	1.11±0.03
F10	26.32 0.06	0.45±0.08	0.548±0.02	17.88±0.03	1.21±0.02
F11	27.07±0.02	0.471±0.04	0.569±0.02	17.22±0.02	1.20±0.04
F12	25.17±0.03	0.459±0.02	0.57±0.02	19.47±0.02	1.24±0.01

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 0.45±0.08to 0.471±0.04 (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 0.5±0.04to 0.569±0.02showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 19.47which shows that the powder has good flow properties.All the formulations has shown the hausners ratio ranging between 1.11 to 1.24 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.

***Invitro* 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	249.39	5.2	0.33	4.10	98.41	59	8
F2	248.66	5.9	0.44	4.99	97.38	62	10
F3	250.99	5.4	0.19	4.23	99.72	35	7
F4	247.24	5.1	0.65	4.34	98.65	46	12
F5	246.92	5.6	0.24	4.19	96.38	26	9
F6	250.33	5.7	0.11	4.33	95.99	19	7
F7	248.19	5.0	0.74	4.77	99.62	34	8
F8	247.4	5.9	0.23	4.34	97.29	20	12
F9	248.41	5.7	0.54	4.13	98.84	43	11
F10	249.99	5.2	0.44	4.81	99.26	56	12
F11	250.2	5.0	0.63	4.72	98.42	21	10
F12	249.79	5.6	0.33	4.23	97.69	62	9

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

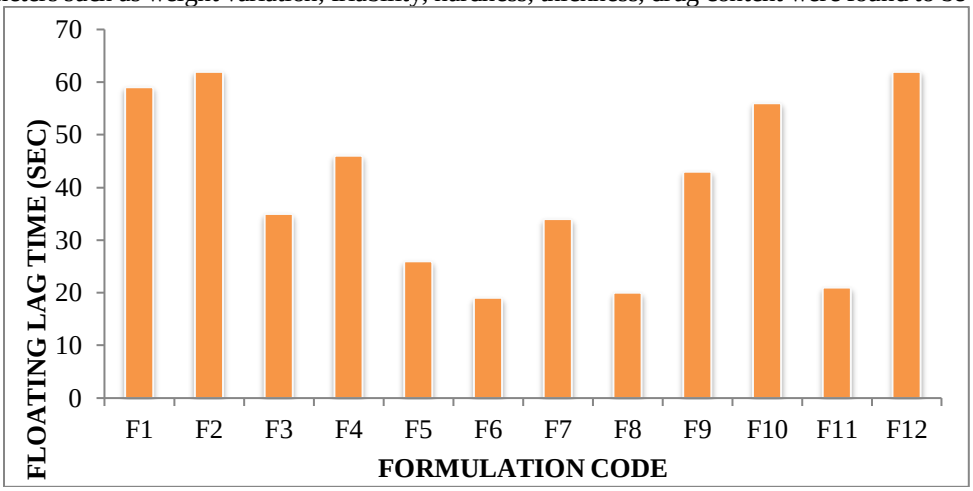

Figure : Floating lag time (Sec)

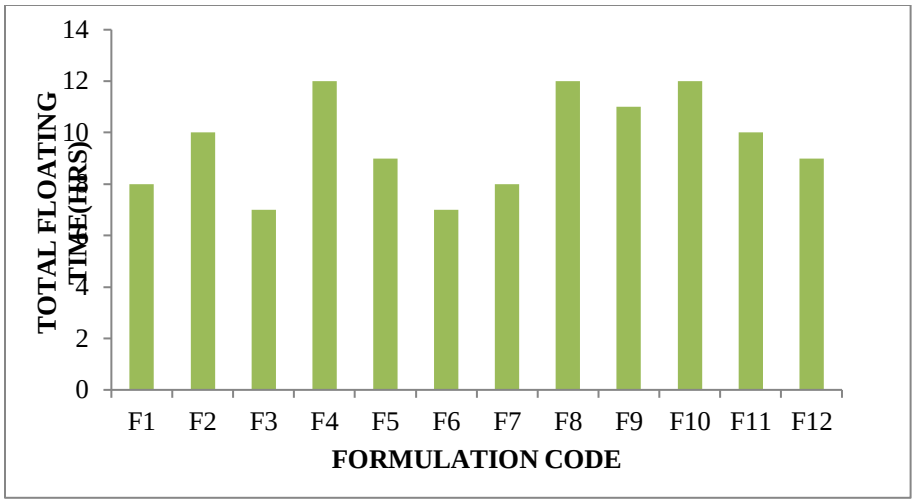

Figure : Total Floating Time (Hrs)

***In Vitro* Drug Release Studies:**

Table no: 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
1	11.59	7.25	10.20	06.35	13.11	15.32	23.85	28.42	14.73	16.42	20.45	15.28
2	26.37	11.31	16.61	10.15	20.56	21.56	36.90	35.61	19.98	24.25	27.91	29.31
3	31.84	18.89	23.85	18.11	26.95	28.71	41.65	40.13	24.86	30.91	33.26	34.86
4	38.56	25.10	32.11	23.91	35.56	32.90	47.23	43.54	28.12	33.59	37.96	41.52
5	47.2	35.51	41.25	32.48	37.71	37.15	52.89	51.32	35.68	47.75	42.85	46.71
6	55.31	41.19	50.86	39.62	42.91	41.86	57.72	58.14	41.10	52.53	50.64	53.86
7	62.50	46.87	56.20	48.37	46.30	48.75	60.98	62.80	46.27	59.70	56.48	56.24
8	67.14	53.96	61.46	52.75	53.26	53.96	62.54	68.51	53.79	63.21	61.31	60.87
9	73.86	56.24	65.82	57.12	58.22	56.26	64.15	72.47	69.46	68.48	65.16	66.65
10	85.41	62.31	74.72	66.48	61.38	64.87	75.12	74.71	79.60	71.22	73.62	71.23
11	89.92	72.75	78.95	69.14	68.55	75.96	77.28	86.25	84.76	80.38	77.19	75.54
12	98.86	78.23	81.54	73.95	71.67	80.42	86.19	99.41	96.82	85.90	82.37	78.21

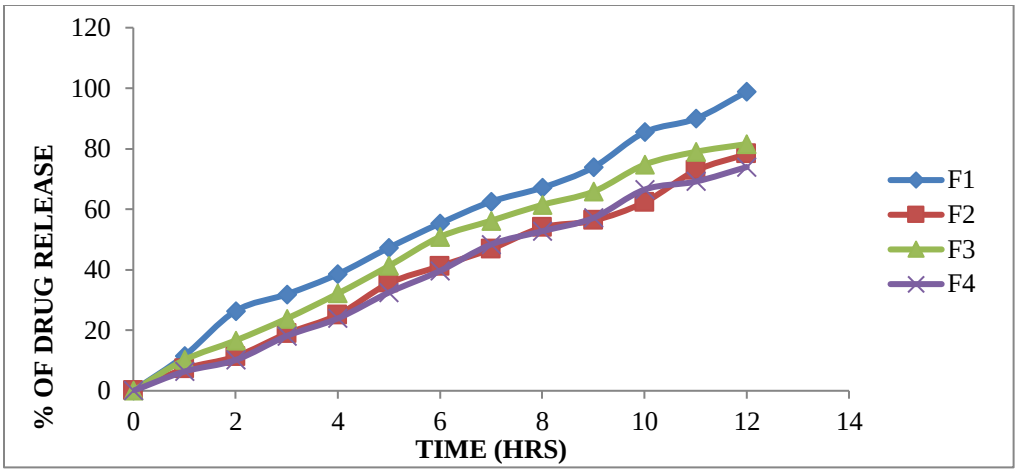

Fig : Dissolution data of Atenolol Floating tablets containing HPMC K4M

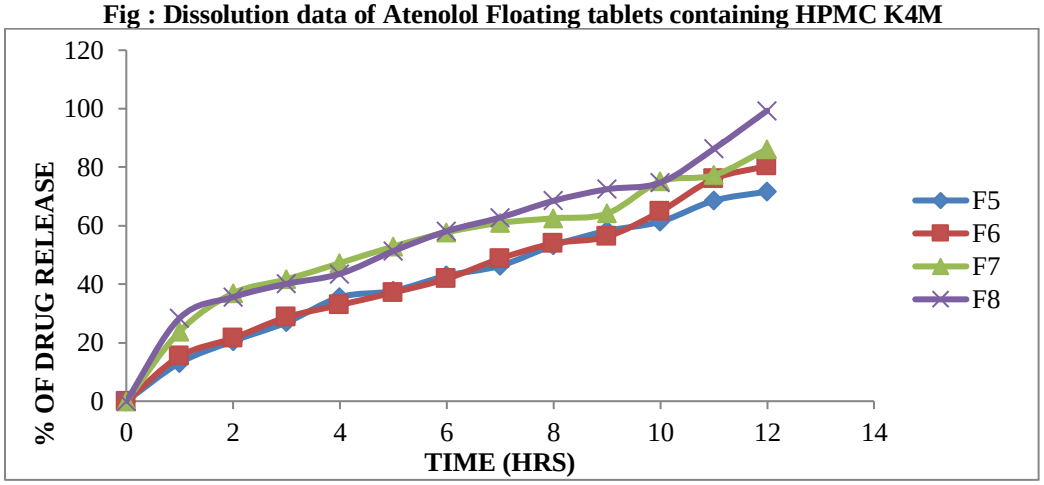

Fig : Dissolution data of Atenolol Floating tablets containing HPMC K15M

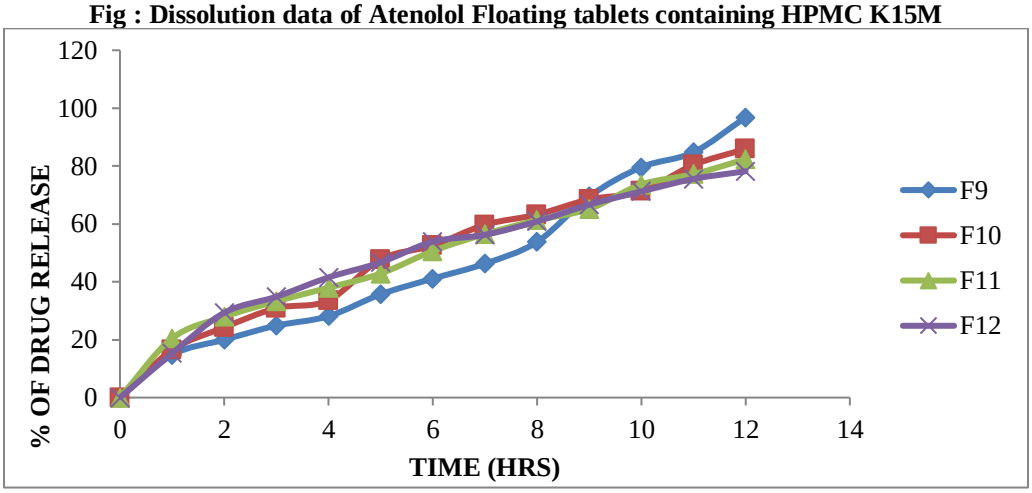

Fig: Dissolution data of Atenolol Floating tablets containing HPMC K100M

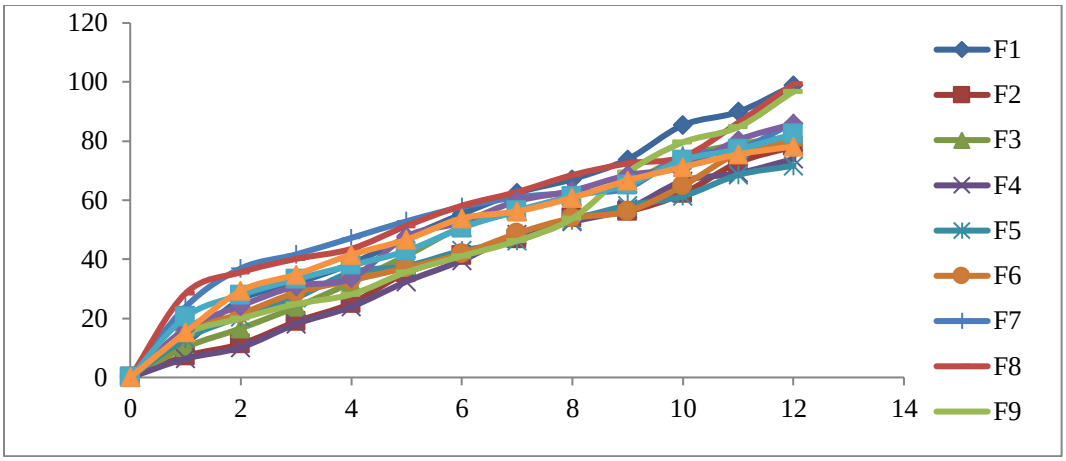

Fig: Dissolution data of Atenolol Floating tablets containing All formulations (HPMC K4M, HPMC K15M, HPMC K100M)

From the dissolution data it was evident that the formulations prepared with HPMC K4M as polymer were retarded the drug release more than 12 hours.
Whereas the formulations prepared with HPMC K15M retarded the drug release up to 12 hours in the concentration 80mg. In higher concentrations the polymer was retard the drug release.
Whereas the formulations prepared with HPMC K100M retarded the drug release up to 12 hours in the concentration 20 mg. In higher concentrations the polymer was unable to retard the drug release.

Hence from the above dissolution data it was concluded that F8 formulation was considered as optimised formulation because good drug release (99.34%) in 12hours.

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

Table No 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
28.42	1	1.000	1.454	0.000	1.855	28.420	0.0352	-0.546	71.58	4.642	4.152	0.490
35.61	2	1.414	1.552	0.301	1.809	17.805	0.0281	-0.448	64.39	4.642	4.008	0.633
40.13	3	1.732	1.603	0.477	1.777	13.377	0.0249	-0.397	59.87	4.642	3.912	0.730
43.54	4	2.000	1.639	0.602	1.752	10.885	0.0230	-0.361	56.46	4.642	3.836	0.805
51.32	5	2.236	1.710	0.699	1.687	10.264	0.0195	-0.290	48.68	4.642	3.651	0.990
58.14	6	2.449	1.764	0.778	1.622	9.690	0.0172	-0.236	41.86	4.642	3.472	1.169
62.8	7	2.646	1.798	0.845	1.571	8.971	0.0159	-0.202	37.2	4.642	3.338	1.303
68.51	8	2.828	1.836	0.903	1.498	8.564	0.0146	-0.164	31.49	4.642	3.158	1.484
72.47	9	3.000	1.860	0.954	1.440	8.052	0.0138	-0.140	27.53	4.642	3.020	1.622
74.71	10	3.162	1.873	1.000	1.403	7.471	0.0134	-0.127	25.29	4.642	2.935	1.706
86.25	11	3.317	1.936	1.041	1.138	7.841	0.0116	-0.064	13.75	4.642	2.396	2.246
99.41	12	3.464	1.997	1.079	-0.180	8.278	0.0101	-0.003	0.66	4.642	0.871	3.771

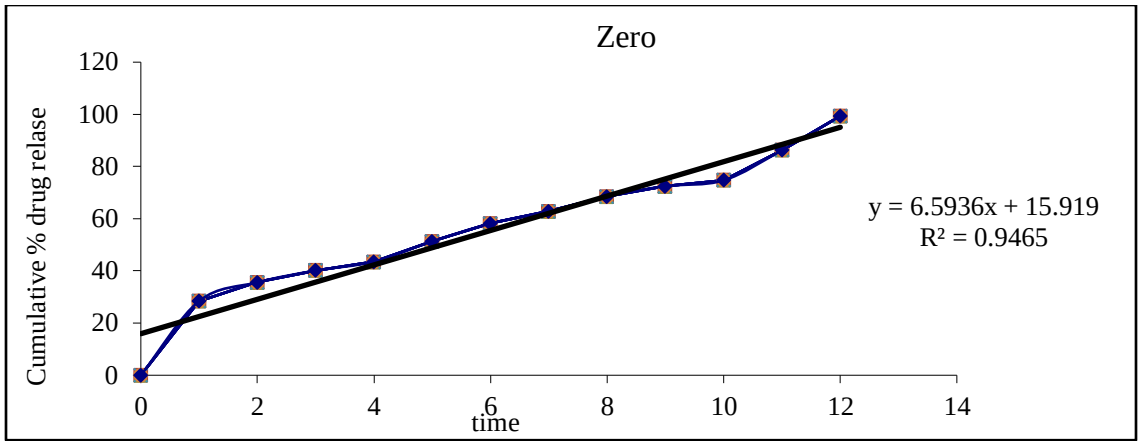

Fig no: Zero order release kinetics

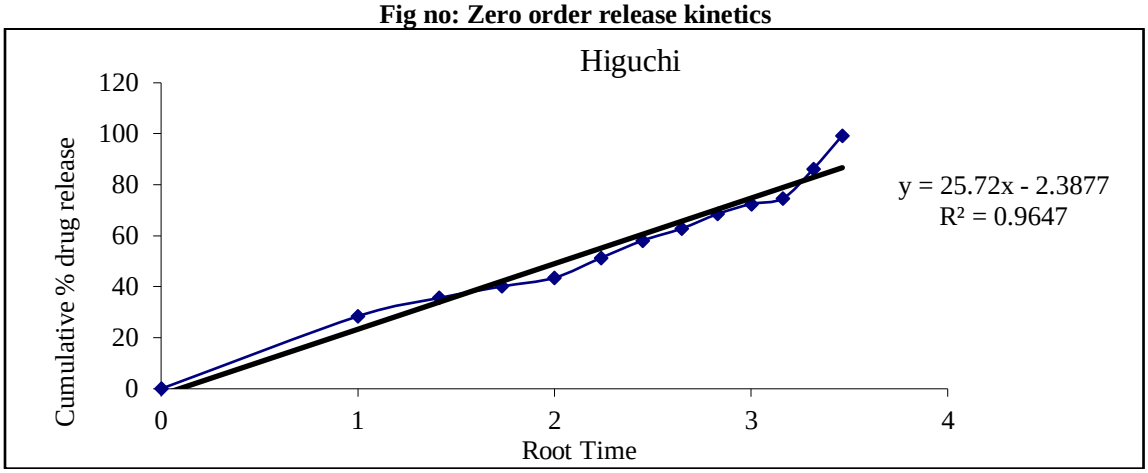

Fig no: Higuchi release kinetics

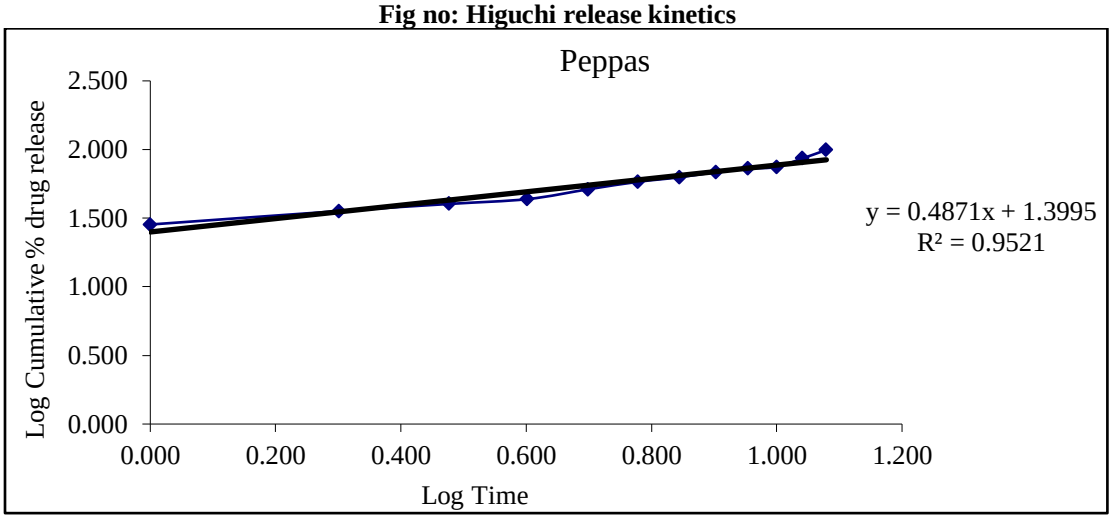

Fig : Kors mayer peppas release kinetics

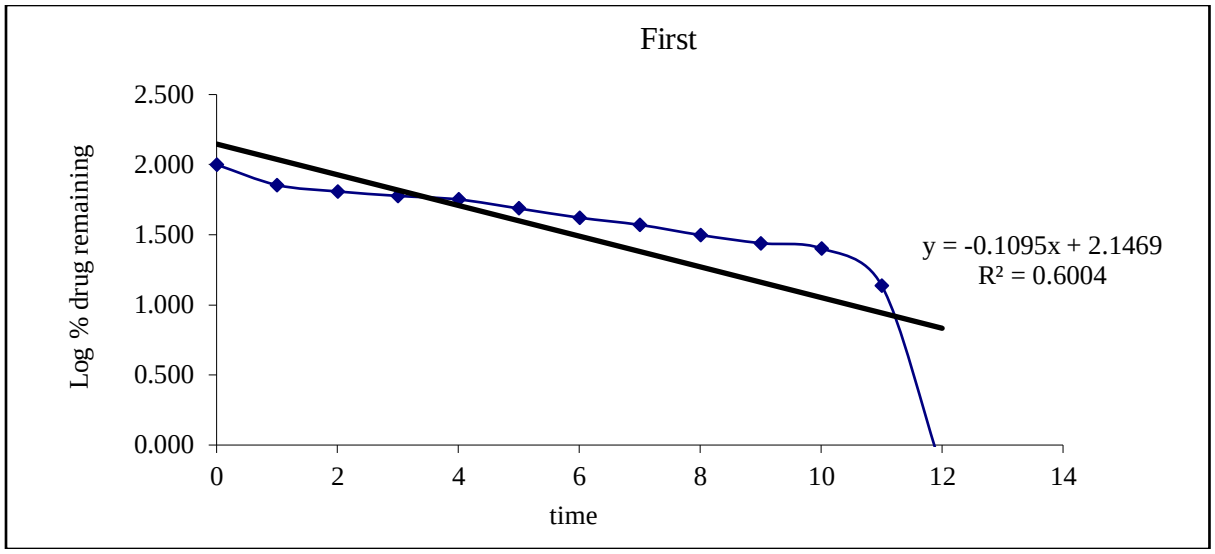

Fig : First order release kinetics

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.

Drug – Excipient compatibility studies

Fourier Transform-Infrared Spectroscopy:

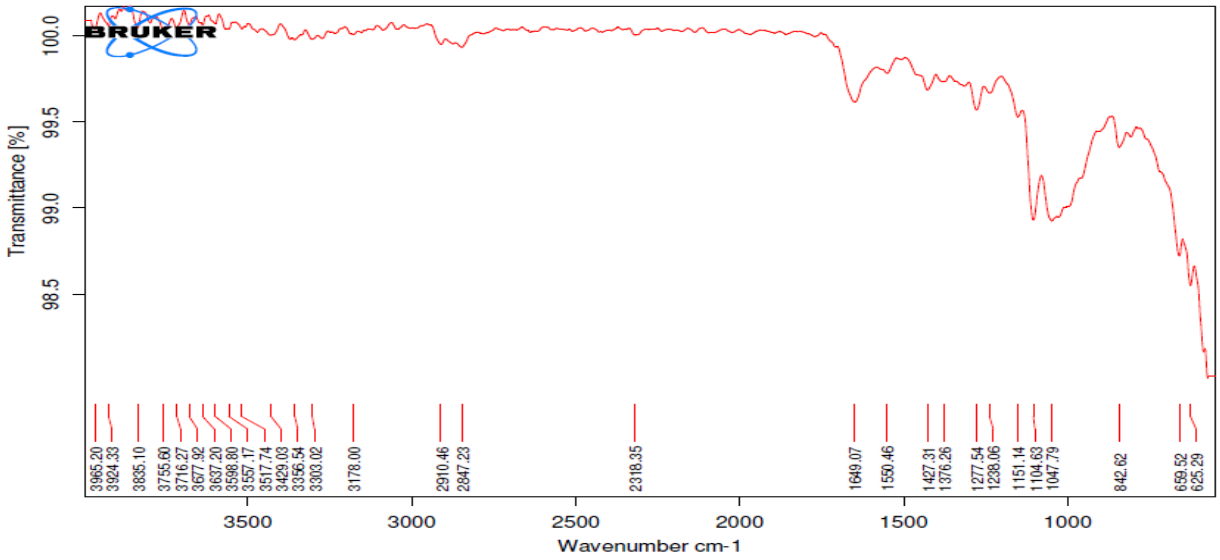

Figure: FTIR Spectrum of pure drug

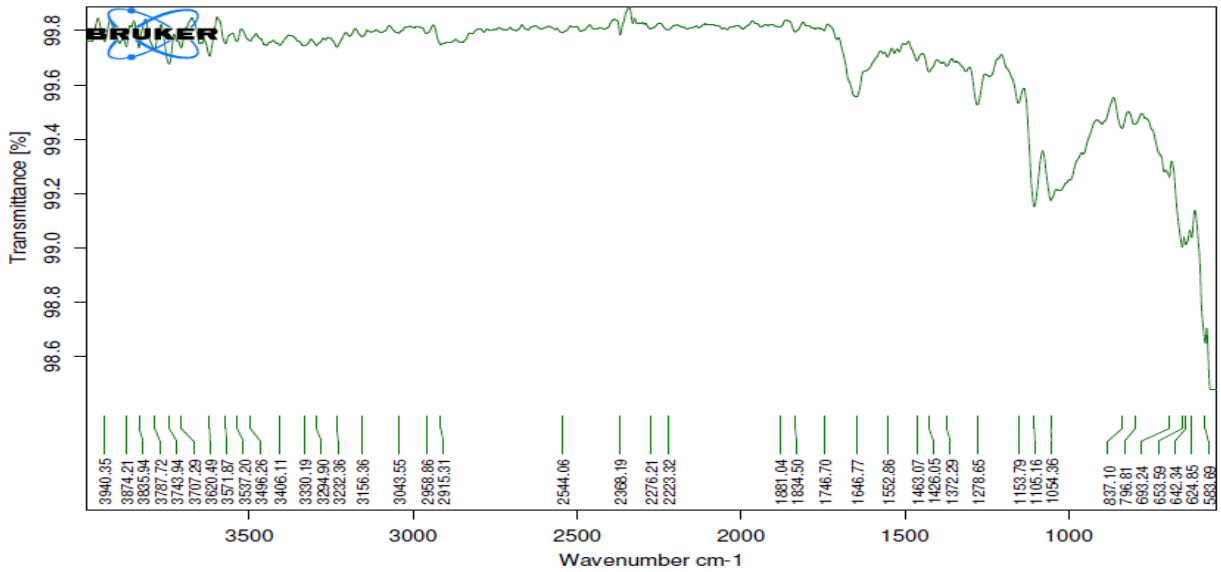

Fig: FTIR Spectrum of optimised formulation

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.

Atenolol 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:

Over the years, various attempts have been made to control the time course of drug in the body through a variety of drug modifications and dosage forms. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the gastrointestinal tract is to control the GRT.

The approach of the present study was to formulate floating tablets of Atenolol and hence for the evaluate the release profiles of these formulations. From the results obtained in the present study, the following conclusions are drawn:

- ✓ The IR spectrum of pure drug and drug-polymer mixture revealed that there was no interaction between polymer and drug. The prepared floating tablets are industrially feasible method.
- ✓ Bulk density and tapped density shown good pack ability, and Carr's index results shown excellent compressibility.
- ✓ Formulation F8 containing 80 mg of HPMC K15M was found to release a maximum of 99.41% at the 12th hour.
- ✓ Comparison of all formulations of Atenolol revealed the fact that developed formulation F8 showed comparable release characteristics, and thus, it may have fair clinical efficacy. Hence, the formulation F8 has met the objectives of the present study.

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