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Formulation & in-vitro evaluation of Imatinib mesylate floating tablet using different polymers

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ABSTRACT

Aim of the study is to formulate and evaluate Imatinib floating tablets using different polymers Sodium alginate, Guar gum, HPMC K100M, and Sod. Bicarbonate, Mg.stearate, Talc in different ratios. The Analytical method development was done on the drugs molecule for gastro retentive floating matrix formulation of Imatinib mesylate by using various hydrophilic polymers. Gas generating agent sodium bicarbonate concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various grades of HPMC. The formulation blend was subjected to various pre-formulation 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 formulations prepared by using HPMC K4M were unable to produce desired drug release; they were unable to retard drug release up to 12 hours. The formulations prepared with Sodium alginate retarded the drug release up to 12 hours in the concentration of 100 mg (F9).The formulations prepared with HPMC K100M were also retarded the drug release for more than 12 hours. The optimized formulation dissolution data was subjected to release kinetics; from the release kinetics data it was evident that the formulation followed Higuchi mechanism of drug release.

Keywords: Imatinib mesylate, HPMC Polymers, Floating tablets.

INTRODUCTIO[1 2 3]

Floating Drug Delivery Systems

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost-effective manufacturing process.Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. These immediate release dosage forms have some limitations such as

1) Drugs with short half-life require frequent administration, which increase the chances of missing dose of drug leading to poor patient compliance.
2) A typical peak-valley plasma concentration-time profile is obtained which makes it difficult to attainment of steady state condition.
3) The unavoidable fluctuations in the drug concentration may lead to under medication or overmedication as the C_{SS} values fall or rise beyond the therapeutic range.
4) The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overmedication occurs. In order to overcome the drawbacks of conventional drug

delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.

Gastro retentive Dosage Form (GRDF)

It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to contrl the gastric residence time (GRT), i.e. gastro retentive dosage form (GRDFs or GRDS). GRDFs extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form. The GI tract is always in a state of continuous motility. There are two modes of motility pattern. The digestive mode and inter digestive mode. In case of fasted state an inter digestive series of electrical events occurs in cyclic manner both through stomach and small intestine every 2-3 hr. This electrical activity is termed as inter digestive my electric cycle.

Phase I : Period of no contraction.
Phase II : Period of intermittent contraction.
Phase III : Period of regular contractions at the maximal frequency that migrate distally.
Phase IV : Period of transition between phase III and phase I

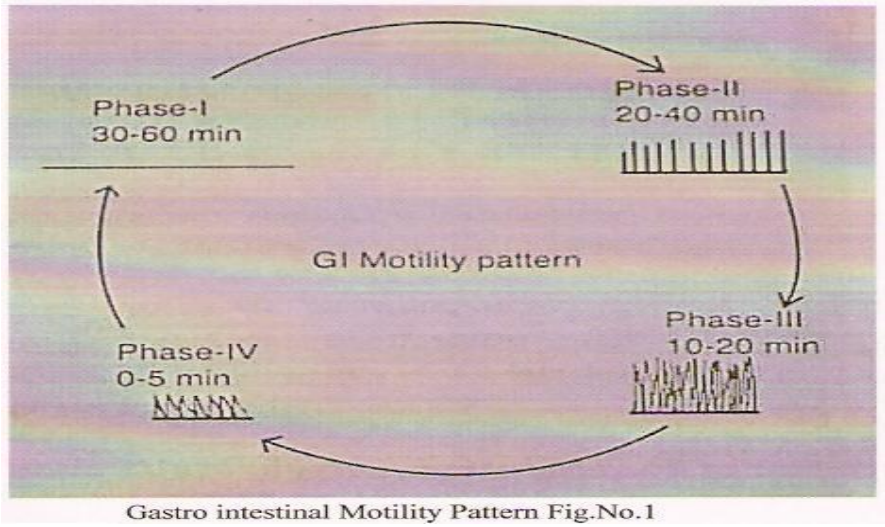


Fig 1: Gastro intestinal motility pattern

PHASE I: The quiescent period, lasts from 30 to 60mins and is characterized by a lack of secretary, electrical and contractile activity.

PHASE II: Exhibits intermittent activity for 20-40 min, during which the contractile motions increase in frequency and size. Bile enters the duodenum during this phase, whereas gastric mucus discharge occurs during the latter part of phase II and throughout phase III.

Phase III: Has a housekeeping role and serves to clear all indigestible materials from the stomach and small intestine. Consequently, a controlled-release gastrointestinal drug delivery system must be capable of resisting the house keeping action of phase III. Studies revealed that in the fed state, the gastric emptying rate is slowed since the onset of MMC is delayed. It can be concluded that feeding results in a lag time before onset of gastric emptying cycle.

PHASE IV: Is the transition period of 0-5mins between Phase III & I.

MATERIALS AND METHODS

Imatinib mesylate, HPMCK100M, Sodium bicarbonate, Mg Stearate, Micro crystalline cellulose, Sodium alginate, TalcWeighing Balance Tablet Compression Machine (Multistation) Hardness tester Vernier calipers, Dissolution Apparatus

METHODOLOGY

Analytical method development

Determination of absorption maxima

A solution containing theconcentration 10 µg/ ml drug was prepared in 0.1N HCl UV spectrum was taken using Double beam UV/VISspectrophotometer. The solution was scanned in the range of 200 – 400.

Preparation calibration curve

100mg of Imatinib pure drug was dissolved in 100ml of water(stock solution)10ml of solution was taken and make up with100ml of water (100µg/ml).from this 10ml was taken and make up with 100 ml of water (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 2,4,6,8,10,20,30,40,50,60,70,80,90 and 100µg/ml of Imatinib per ml of solution. The absorbance of the above dilutions was measured at 231 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.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes.The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by thequality 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 Tablets

All the formulations were prepared by direct compression. The compression of different formulations are given in Table 6.3.The tablets were prepared as per the procedure given below and aim is to prolong the release of Imatinib . Total weight of the tablet was considered as 300mg.

Procedure:

1) Imatinib 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.

Optimization of Sodium bicarbonate concentration

Sodium bicarbonate was employed as effervescent gas generating agent. It helps the formulation to float. Various concentrations of sodium bicarbonate were employed; floating lag time and floating duration were observed. Based on that the concentration of sodium bicarbonate was finalized and preceded for further formulations. Total weight of tablet is 300 mg.

Table 1: Optimization sodium bicarbonate concentration

S.No	Excipient Name	EF1	EF2	EF3	EF4
1	Imatinib	100	100	100	100
2	HPMC K 100M	100	100	100	100
4	$NaHCO_3$	20	40	60	80
5	Mg.stearate	1	1	1	1
5	Talc	1	1	1	1
7	MCC pH 102	Q.S	Q.S	Q.S	Q.S

All the quantities were in mg.

Based on the floating lag time and floating duration the concentration of sodium bicarbonate was optimised.Initially formulations were prepared with HPMC K 4M,Guar gum, and Chitosan. The polymers were Unable to retard the required drug release pattern because the tablets were unable to maintain the tablet integrity and shape also even up to 2 hours. Hence the were not taken into consideration.

Table 2: Formulation composition for floating tablets

Name of ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Imatinib	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**
HPMC K4M	**50**	**75**	**100**												
Chitosan				**50**	**75**	**100**									
Sodium alginate							**50**	**75**	**100**						
HPMC K100M										**50**	**75**	**100**			
Guar gum													**50**	**75**	**100**
$NaHCO_3$	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**
Mag. Stearate	**2.5**	**2.5**	**2.5**	**2.5**	**2.5**	**2.5**	**2.5**	**2.5**	**2.5**	**2.5**	**2.5**	**2.5**	**2.5**	**2.5**	**2.5**
Talc	**2.5**	**2.5**	**2.5**	**2.5**	**2.5**	**2.5**	**2.5**	**2.5**	**2.5**	**2.5**	**2.5**	**2.5**	**2.5**	**2.5**	**2.5**
MCC pH	**QS**	**QS**	**QS**	**QS**	**QS**	**QS**	**QS**	**QS**	**QS**	**QS**	**QS**	**QS**	**QS**	**QS**	**QS**

All the quantities were in mg

Evaluation of post compression parameters for prepared Tablets

The designed formulation compression coated 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

Table 3:Pharmacopoeial specifications for tablet weight variation

Average weight of tablet (mg) (I.P)	Average weight of tablet (mg) (U.S.P)	Maximum percentage difference allowed
Less than 80	Less than 130	10
80-250	130-324	7.5
More than	More than 324	5

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 Meloxicam 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

Dissolution parameters

Apparatus --USP-II, Paddle Method
Dissolution Medium -- 0.1 N HCl
RPM --50
Sampling intervals (hrs) --0.5,1,2,3,4,5,6,7,8,10,11,12
Temperature --37°c ± 0.5°c

As the preparation was for floating drug release given through oral route of administration, different receptors fluids are used for evaluation the dissolution profile.

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 ± 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 receptor fluid and analyzed by spectrophotometrically at 231 nm using UV-spectrophotometer.

RESULTS AND DISCUSSION

The present study was aimed to developing gastro retentive floating tablets of Imatinib mesylate using various HPMC polymers. All the formulations were evaluated for physicochemical properties and invitro drug release studies.

Analytical Method

Standard Graph of Imatinib mesylate was taken in Simulated Gastric fluid (pH 1.2) at 231 nm.

Table 4: Observations for graph of Imatinib in 0.1N HCl (231 nm)

Conc [µg/l]	Abs
2	0.013
4	0.024
6	0.034
8	0.043
10	0.055
15	0.078
20	0.103
30	0.158
40	0.205
50	0.257
60	0.302
70	0.358
80	0.411

90	0.456
100	0.503

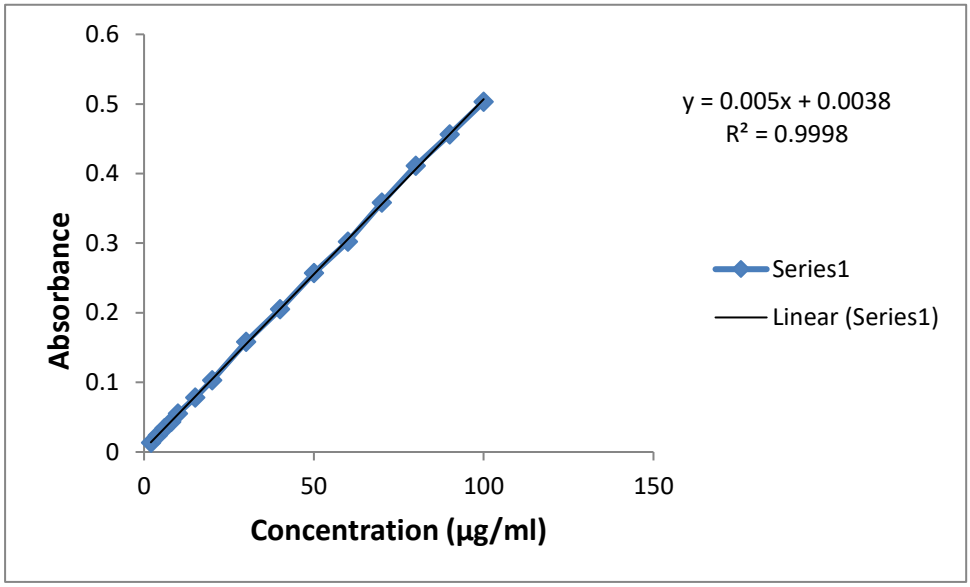


Fig2: Standard graph of Imatinib in 0.1N HCl

Preformulation parameters of powder blend

Table 5: 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	26.01	0.49±0.07	0.57±0.01	16.21±0.06	0.86±0.06
F2	24.8	0.56±0.06	0.62±0.05	16.87±0.05	0.98±0.05
F3	22.74	0.52±0.03	0.68±0.07	17.11±0.01	0.64±0.03
F4	25.33	0.54±0.04	0.64±0.08	17.67±0.08	1.12±0.04
F5	26.24	0.53±0.06	0.67±0.03	16.92±0.04	1.2±0.08
F6	26.12	0.56±0.05	0.66±0.06	17.65±0.09	1.06±0.09
F7	27.08	0.58±0.06	0.69±0.04	16.43±0.05	0.76±0.03
F8	25.12	0.48±0.05	0.57±0.02	17.97±0.02	1.15±0.09
F9	25.45	0.54±0.08	0.62±0.03	17.54±0.09	1.17±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 0.43±0.07 to 0.58±0.06 (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 0.57 to 0.69 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18 which shows that the powder has good flow properties.All the formulations has shown the hausner ratio ranging between 0 to 1.2 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 80 mg concentration showed less floating lag time of 4 min and the tablet was in floating condition for more than 12 hours.

Quality Control 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.

Formulation codes	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Flaoting lag time(min)
F1	302.5	4.1	0.52	2.8	99.76	4.0
F2	305.4	4.2	0.54	2.9	99.45	4.2
F3	308.6	4.2	0.51	2.9	99.34	4.5
F7	299.6	4.1	0.55	2.9	99.87	4.1

F8	299.4	4.2	0.56	2.7	99.14	4.0
F9	298.7	4.2	0.45	2.5	98.56	4.4

Invitro quality control parameters for selected formulations

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

In-Vitro Drug Release Studies

Table 6: Dissolution Data of Imatinib mesylate Tablets Prepared With HPMCK4M In Different Concentrations

TIME(hr)	CUMULATIVE PERCENT DRUG DISSOLVED (n=3±SD)		
	F1	**F2**	**F3**
0.5	21.73	18.52	19.53
1	59.23	37.47	28.97
2	84.9	59.93	35.89
3	94.873	65.85	45.7
4	94.873	77.54	54.38
5	-	89.55	61.2
6	-	96.6	67.06
7	-	-	72.52
8	-	-	77.88
9	-	-	86.6
10	-	-	89.09
11	-	-	94.52

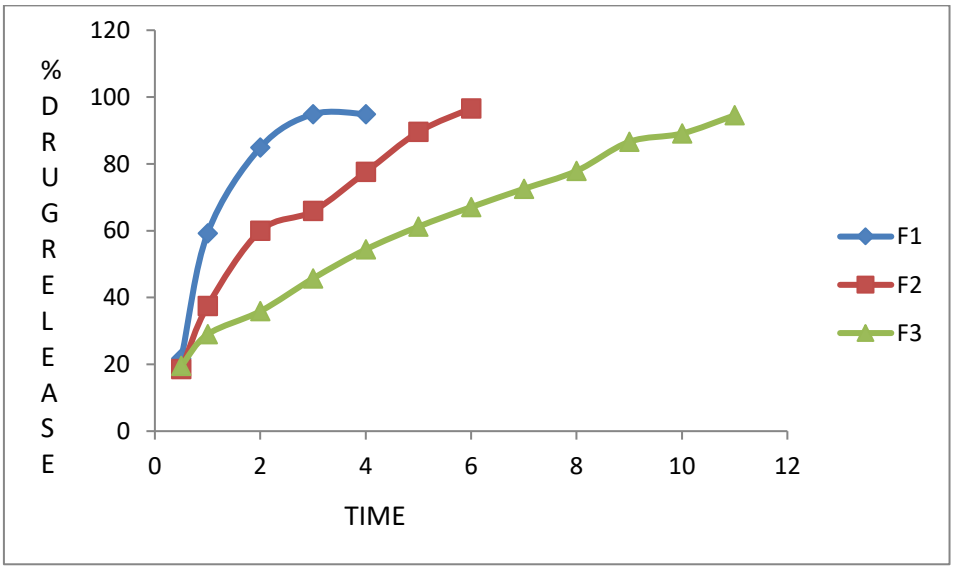


Fig 3: Dissolution profile of Imatinib floating tablets (F1, F2, F3 formulations).

Table 7: Dissolution Data of Imatinib Tablets Prepared With Sodium alginate In Different Concentrations

TIME	CUMULATIVE PERCENT DRUG DISSOLVED (n=3±SD)		
(hr)	**F4**	**F5**	**F6**
0.5	18.45	18.42	19.62
1	36.26	27.73	27.86
2	52.16	35.63	36.35
3	70.01	42.04	41.45
4	87.26	57.25	47.80
5	93.10	64.33	55.25
6		75.41	60.24
7		83.84	66.73

8	92.80	71.34
9		78.52
10		80.17
11		88.75
12		96.33

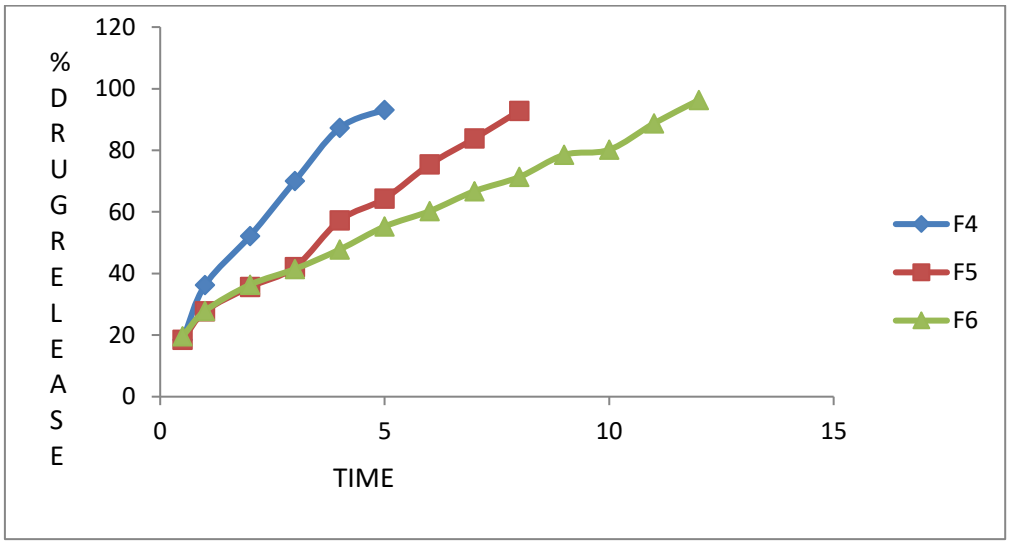


Fig4: Dissolution profile of Imatinib floating tablets (F4, F5, F6formulations).

Table 8: Dissolution Data of Imatinib Tablets Prepared With HPMC K100M In Different Concentrations

TIME **(hr)**	**CUMULATIVE PERCENT DRUG DISSOLVED (n=3±SD)**		
	F7	**F8**	**F9**
0.5	18.81	19.89	14.21
1	29.02	28.04	18.87
2	35.70	35.43	27.19
3	43.32	41.65	35.66
4	49.25	47.18	43.32
5	55.28	53.81	51.06
6	60.92	58.89	57.13
7	66.08	64.53	63.63
8	70.44	69.43	69.71
9	77.22	72.83	73.34
10	80.90	79.98	79.27
11	87.83	83.52	82.86
12	91.90	88.65	85.97

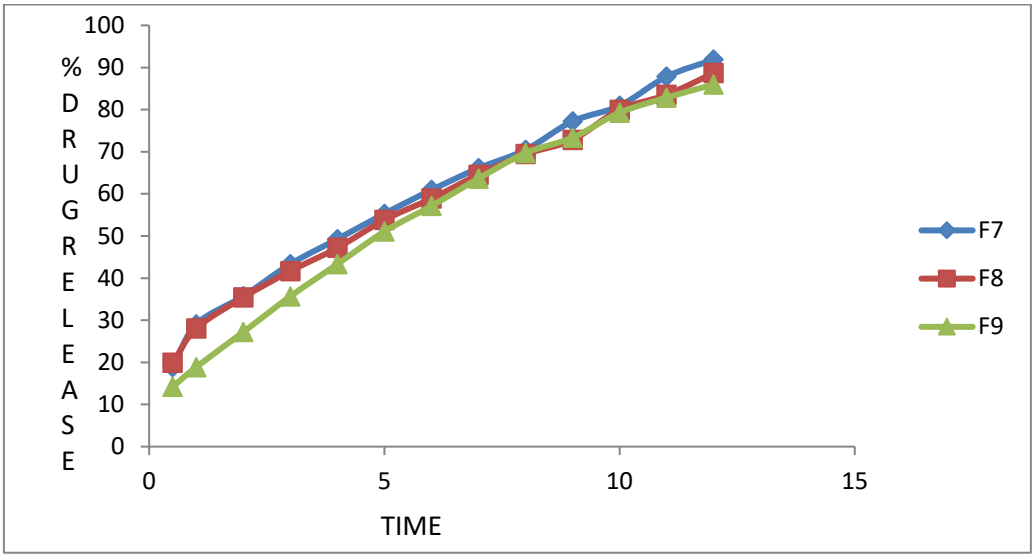


Fig 5: Dissolution profile of Imatinib floating tablets (F7, F8, F9 formulations)

From the dissolution data it was evident that the formulations prepared with HPMC K4 M as polymer were unable to retard the drug release up to desired time period i.e., 12 hours. Whereas the formulations prepared with Sodium alginate retarded the drug release in the concentration of 100 mg showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 96.33 % in 12 hours with good floating lag time and floating buoyancy time.The formulations prepared with HPMC K 100M showed more retardation even after 12 hours they were not shown total drug release. Hence they were not considered.

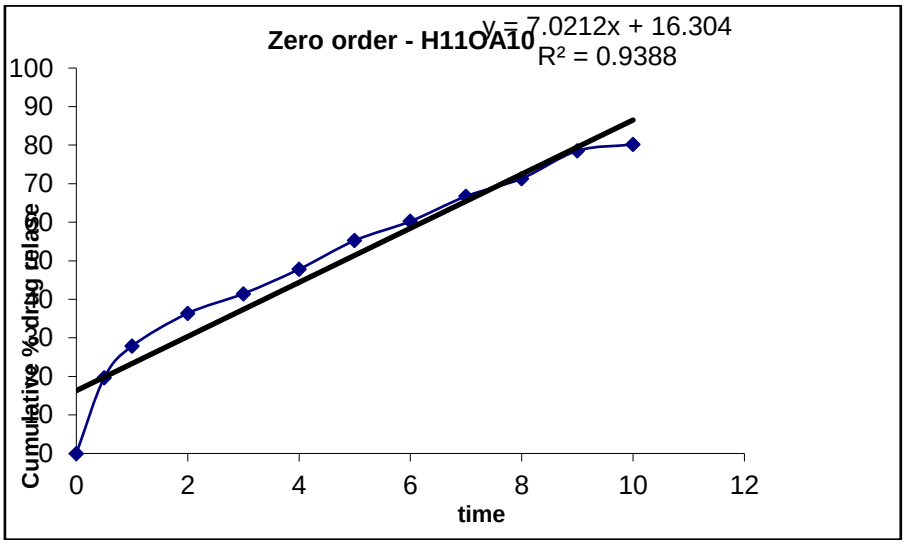


Fig 6 : Zero order release kinetics graph

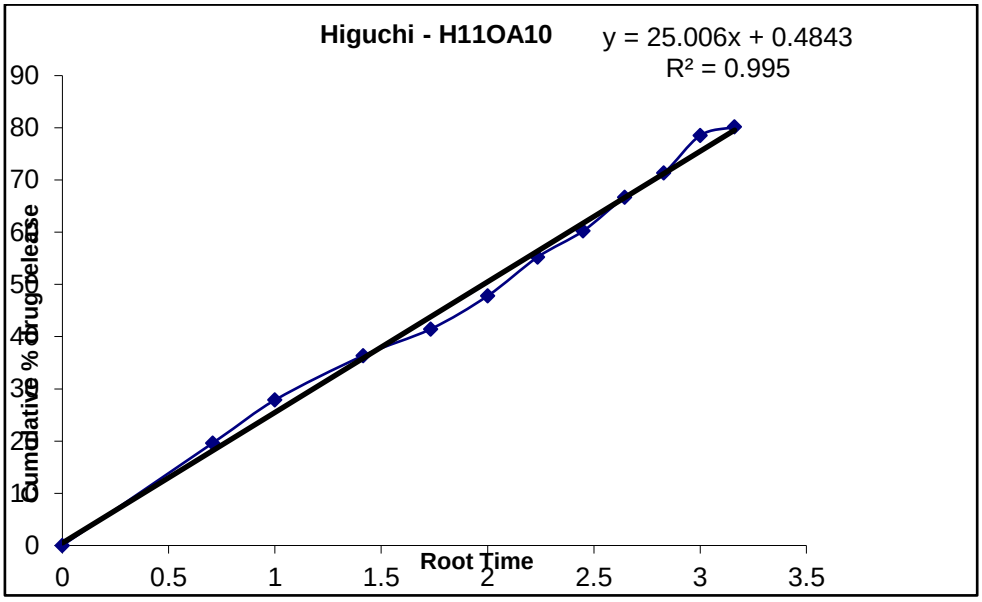


Fig 7: Higuchi release kinetics graph

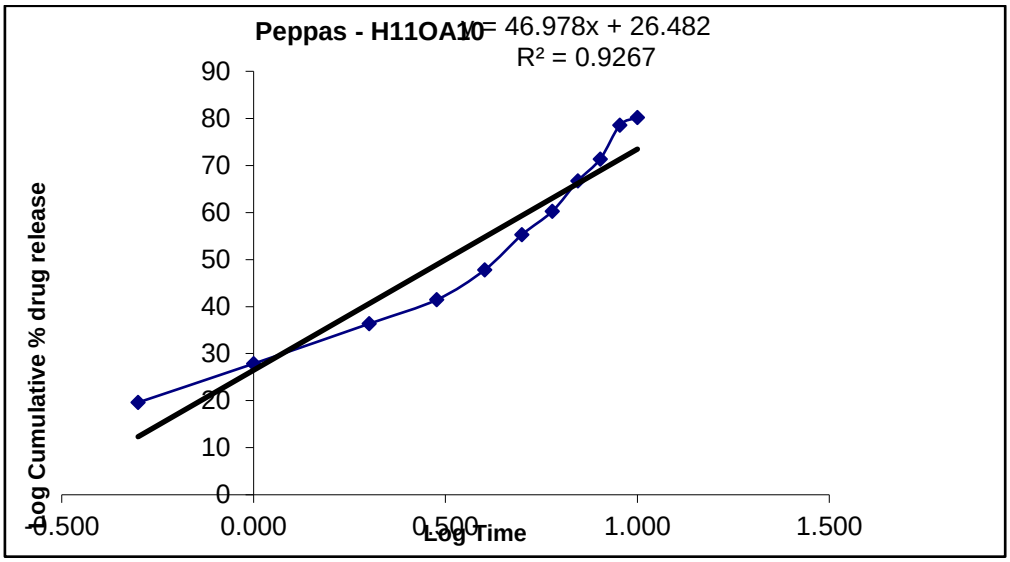
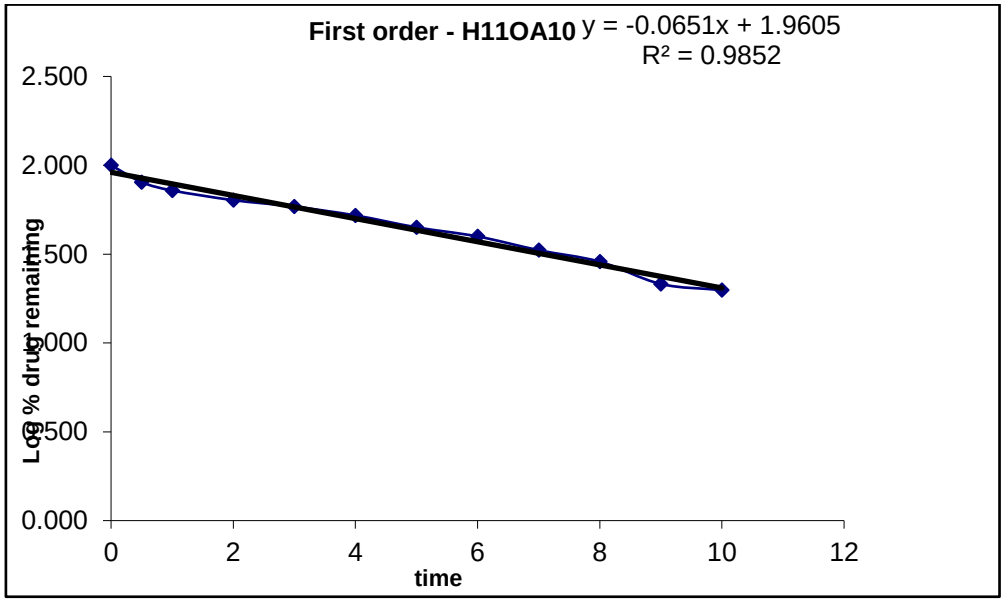


Fig 8: Kars mayerpeppas graph



From the above graphs it was evident that the formulation F9 was followed Higuchi mechanism.

Fig 9: First order release kinetics graph

CONCLUSION

In the present research work gastro retentive floating matrix formulation of Imatinib by using various hydrophilic polymers. 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. Then the formulation was developed by using different concentrations of polymers of various grades of HPMC. The formulation blend was subjected to various pre-formulation 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 formulations prepared by using HPMC K4M were unable to produce desired drug release, they were unable to retard drug release up to 12 hours. The formulations prepared with Sodium alginate retarded the drug release up to 12 hours in the concentration of 100 mg (F9).The formulations prepared with HPMC K100M were also retarded the drug release for more than 12 hours. Hence they were not considered. The optimized formulation dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed Higuchi mechanism of drug release.

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