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Research

Formulation and evaluation of floating controlled release tablets of imatinib mesylate using hydrophilic matrix system.

Maddimsetty Yesu Surya Prakash*[1], B. Deekshi Gladiola [1], Adapa. Venkateswara Rao [1]

[1]*Department of Pharmaceutics, Pydah College of Pharmacy Patavala, Andhra University, Kakinada, Andhra Pradesh, India*

*Author for Correspondence: Maddimsetty Yesu Surya Prakash
Email: suresh02405@gmail.com

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Abstract

The present investigation concerns the development of floating drug delivery system of Imatinib Mesylate which is to increase the gastric residence time thus prolonging the drug release with localized drug action .Floating tablets were prepared with direct compression method by using different polymers with ratios. The prepared Floating Tablets were evaluated for various parameters like Hardness, Thickness, Friability, Uniformity of drug content, Invitro floating studies and In vitro drug release. All the Floating tablets were showed good results. Amongall IM4 formulation showed good drug release of 99.87% for 12hrs.

Keywords: Imatinib Mesylate, Floating Controlled Tablets.

INTRODUCTION

Oral controlled drug delivery system

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, patientacceptance and cost-effective manufacturing process[1]. Pharmaceutical products were designed for oral delivery are mainly conventional drug delivery systems, which given immediate release of drug for rapidabsorption. These immediate release dosage forms have some limitations such as[2, 3]:

- Drugs with short half-life require frequent administration, which increase the chances of missing dose of drug leading to poor patient compliance.
- A typical peak-valley plasma concentration-time profile is obtained which makesattainment of steady state condition difficult.
- 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.

- The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overmedicationoccurs.

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[4].

Controlled Drug Delivery Systems

Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue[5].Controlled drug delivery or modified drug delivery systems are conveniently divided into four categories.

1) Delayed release
2) Sustained release
3) Site-specific targeting
4) Receptor targeting

More precisely, Controlled delivery can be defined as[6]: -

1) Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.
2) Localized drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue.
3) Targeted drug action by using carriers or chemical derivatives to deliver drugto a particular target cell type.
4) Provide a physiologically/therapeutically based drug release system. In other words, the amount and the rate of drug release are determined by the physiological/ therapeutic needs of the body.

A controlled drug delivery system is usually designed to deliver the drug at particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug. Controlled drug delivery usually results in substantially constant blood levels of the active ingredient as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient.

Oral Controlled Drug Delivery Systems

Oral controlled release drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either local or systemic action. All the pharmaceutical products formulated for systemic delivery via the oral route of administration, irrespective of the mode of delivery (immediate, sustainedor controlled release) and the design of dosage form (solid dispersion or liquid),must be developed within the intrinsic characteristics of GI physiology. Thereforethe scientific framework required for the successful development of oral drug delivery systems consists of basic understanding of (i) Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug (ii) the anatomic and physiologic characteristics of the gastrointestinal tract and (iii) physicochemical characteristics and the drug delivery mode of the dosage form to be designed.

The main areas of potential challenge in the development of oral controlled drug delivery systems are[9]: -

- Development of a drug delivery system: To develop a viable oral controlled release drug delivery system capable of delivering a drug at a therapeutically effective rate to a desirable site for duration required for optimal treatment.
- Modulation of gastrointestinal transit time: To modulate the GI transit timeso that the drug delivery system developed can be transported to a target site or to the vicinity of an absorption site and reside there for a prolonged periodof time to maximize the delivery of a drug dose.
- Minimization of hepatic first pass elimination: If the drug to be delivered is subjected to extensive hepatic first-pass elimination, preventive measures should be devised to either bypass or minimize the extent of hepatic metabolic effect.

Conventional oral controlled dosage forms suffer from mainly two adversities[10]. The short gastric retention time (GRT) and unpredictable gastric emptying time (GET). A relatively brief GI transit time of most drug products impedes the formulation of single daily dosage forms. Altering the gastric emptying can overwhelm these problems. Therefore it is desirable, to formulate a controlled release dosage form that gives an extended GI residence time.

Extended release dosage form with prolonged residence time in stomach are highly desirable for drugs[11,12].

- That are locally active in stomach.
- That have an absorption window in the stomach or in the upper small intestine.
- That are unstable in the intestinal or colonic environment

- Have low solubility at high pH values.

MATERIALS

Imatinib Mesylate-Procured From Mylan, Hyderabad. Provided by SURA LABS, Dilsukhnagar, Hyderabad, HPMC K100-Elder Pharmaceuticals Pvt Ltd, Dehradun (India), Carbopol-934-Elder Pharmaceuticals Pvt Ltd, Dehradun (India), Polyvinyl alcohol-Elder Pharmaceuticals Pvt Ltd, Dehradun (India), Sodium bicarbonate-Merck Specialities Pvt Ltd, Mumbai, India, Citric acid-Merck Specialities Pvt Ltd, Mumbai, India, Talc-S.D. Fine Chem. Ltd. Mumbai, Mg sterate-S.D. Fine Chem. Ltd. Mumbai, Lactose-S.D. Fine Chem. Ltd. Mumbai.

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 Imatinib Mesylate pure drug was dissolved in 10ml of methanol (stock solution1) from stock solution1. 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 255nm 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 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}.

Pre formulation 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

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. 10 gm powder blend was sieved and introduced into a dry 20 ml 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 than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, 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 poorer flowing materials, there are frequently greater interparticle interactions, and a 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

For optimization of sodium bicarbonate concentration, granules were prepared by direct compression method.

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.

Optimization of Sodium bicarbonate

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 the concentration of sodium bicarbonate was finalised and preceded for further formulations.

Table 1: Optimisation sodium bicarbonate concentration

Ingredients	DO1	DO2	DO3
Imatinib Mesylate	100	100	100
Carbopol-934	25	50	75
$NaHCO_3$	15	15	15
Citric Acid	10	10	10
Mg.Stearate	5	5	5
Talc	5	5	5
Lactose	240	215	190
Total weight	400	400	400

All the quantities were in mg.

Based on the floating lag time and floating duration the concentration of sodium bicarbonate was optimised.

Formulation of tablets

Table 2: Formulation composition for Floating tablets

Ingredients	IM1	IM2	IM3	IM4	IM5	IM6	IM7	IM8	IM9
Imatinib Mesylate	100	100	100	100	100	100	100	100	100
HPMC K100	25	50	75	-	-	-	-	-	-
Carbopol-934	-	-	-	25	50	75	-	-	-

Polyvinyl alcohol	-	-	-	-	-	-	25	50	75
Sodium bicarbonate	15	15	15	15	15	15	15	15	15
Citric acid	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5
Mg sterate	5	5	5	5	5	5	5	5	5
Lactose	240	215	190	240	215	190	240	215	190
Total wt	400	400	400	400	400	400	400	400	400

All the quantities were in mg

RESULTS AND DISCUSSION

Analytical Method

Determination of absorption maxima : The standard curve is based on the spectrophotometry. The maximum absorption was observed at 255 nm.

calibration curve: Graphs of Imatinib Mesylate was taken in 0.1N HCL (pH 1.2).

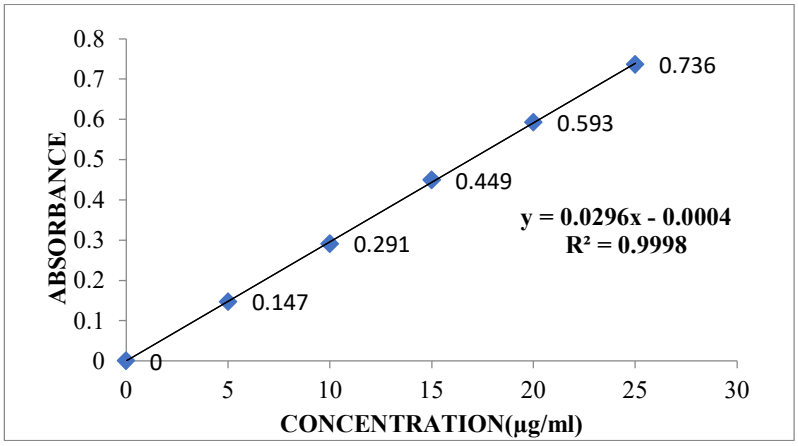

Fig 1: Standard graph of Imatinib Mesylate in 0.1N HCL

Standard graph of Imatinib Mesylate was plotted as per the procedure in experimental method and its linearity is shown in Table and Fig. The standard graph of Imatinib Mesylate showed good linearity with R^2 of 0.9998, which indicates that it obeys "Beer- Lamberts" law.

Drug – Excipient compatability studies

Fourier Transform-Infrared Spectroscopy

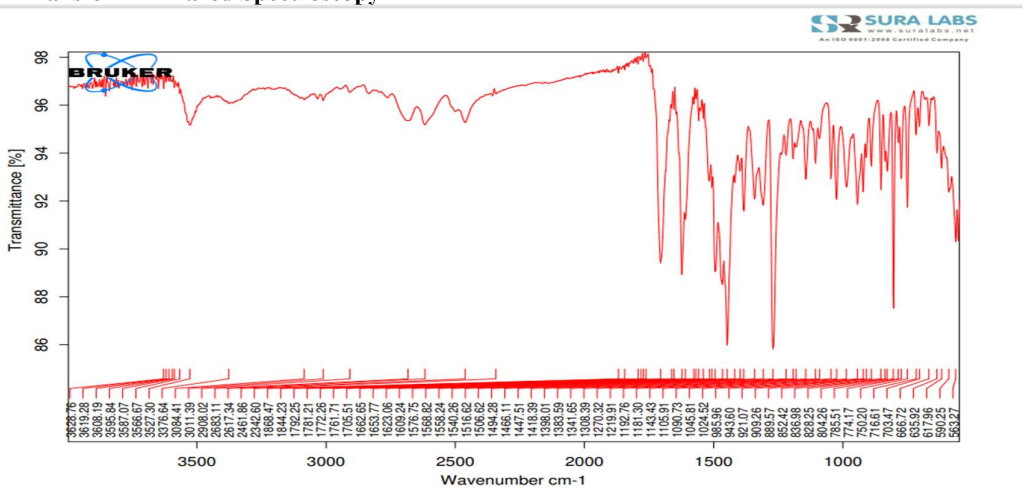

Fig 2: FTIR Spectrum of pure drug

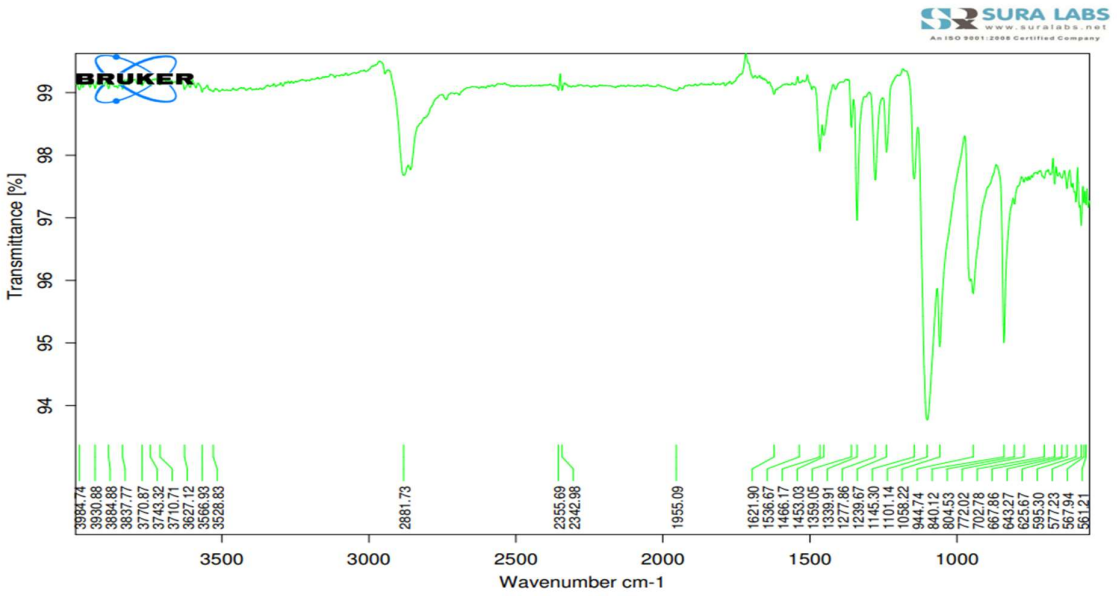

Fig 3: FTIR Spectrum of optimised formulation

From the FTIR data it was evident that the drug and excipients doses not have any interactions. Hence they were compatible.

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
IM1	28.36	0.46	0.54	14.81	1.19
IM2	25.64	0.42	0.63	30.15	1.50
IM3	27.02	0.44	0.54	18.05	1.22
IM4	24.22	0.52	0.57	8.77	1.09
IM5	31.38	0.57	0.63	9.52	1.10
IM6	24.22	0.46	0.57	19.29	1.23
IM7	30.11	0.42	0.52	19.23	1.23
IM8	22.29	0.52	0.60	13.33	1.15
IM9	27.02	0.48	0.57	18.75	1.08

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 0.42 to 0.57 (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 0.52 to 0.63 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 by direct compression method and three more formulations were prepared by Direct Compression method to compare the floating buoyancy. The formulation containing sodium bicarbonate in 15 mg, Citric Acid in 10mg concentration showed less floating lag time in Direct Compression method 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, Drug content and drug release studies were performed for floating tablets.

Table 4: *In vitro* quality control parameters

Formulation codes	Average Weight (mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Flaoting lag time (min)	Total Floating Time (Hrs)
IM1	399.22	4.87	0.18	2.36	98.93	6.37	12
IM2	398.39	4.53	0.26	2..48	99.88	3.92	12
IM3	399.12	4.92	0.17	2.55	97.62	5.22	12
IM4	400.71	4.57	0.13	2.32	99.51	2.11	11
IM5	401.65	4.63	0.35	2.28	99.49	4.31	12
IM6	398.48	4.55	0.22	2.54	98.62	5.61	12
IM7	400.95	4.83	0.37	2.47	97.89	4.48	12
IM8	399.36	4.64	0.29	2.43	99.57	3.63	12
IM9	398.24	4.59	0.25	2.51	98.38	4.27	12

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

***In Vitro* Drug Release Studies**

Table 5: Dissolution data of Floating Tablets (IM1- IM3)

TIME	CUMULATIVE PERCENT DRUG RELEASED								
(hr)	IM1	IM2	IM3	IM4	IM5	IM6	IM7	IM8	IM9
0	0	0	0	0	0	0	0	0	0
0.5	9.14	15.41	11.57	19.61	22.15	16.65	14.94	16.59	12.34
1	13.15	20.22	17.39	27.74	28.91	25.85	23.67	25.11	18.95
2	17.84	26.69	23.12	36.21	38.87	36.55	37.28	33.65	29.64
3	20.65	34.95	29.82	45.15	47.91	46.14	42.31	42.54	35.27
4	23.58	41.32	37.65	52.97	55.14	55.48	49.57	45.16	42.22
5	25.87	47.29	43.55	59.64	64.56	68.62	53.64	51.39	49.17
6	28.67	55.64	49.87	63.81	63.11	74.32	59.32	55.16	53.31
7	31.95	60.65	59.31	69.77	68.38	78.21	64.12	61.31	57.69
8	36.87	65.96	62.99	74.31	72.87	79.92	73.45	66.87	62.28
9	47.88	71.58	69.39	85.90	80.54	85.10	76.38	78.91	73.66
10	52.45	75.32	75.84	89.39	85.64	98.26	80.87	81.74	77.49
11	58.22	81.99	80.55	95.68	90.39	92.36	88.39	86.12	82.83
12	75.57	84.15	85.88	99.87	93.49	94.61	91.14	89.58	85.28

From the dissolution data, it was revealed that formulations prepared with HPMC K100. Used IM1- IM3 formulation did not retard the drug release up to 12 hrs. Hence those formulation did not take into consideration. Where as IM3 Formulation showed Good Drug Release (85.88%) in 12 hours. Formulations prepared with Carbopol-934 IM4 – IM6 Formulations Does not retard the drug release upto 12hrs. These formulations also did not take into consideration. In that IM4 Formulation Showed better drug release (99.87%) in 12 hours. Formulations prepared with Polyvinyl alcohol IM7– IM9 Formulations Does not retard the drug release upto 12hrs. These formulations also did not take into consideration. In that IM7Formulation Showed better drug release (91.14%) in 12 hours. Among all formulations IM4 formulation was considered as optimised formulation. It was shown 99.87% drug release at 12hrs.

Application of Release Rate Kinetics to Dissolution Data for optimised formulation

Table 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	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
19.61	0.5	0.707	1.292	-0.301	1.905	39.220	0.0510	-0.708	80.39	4.642	4.316	0.326
27.74	1	1.000	1.443	0.000	1.859	27.740	0.0360	-0.557	72.26	4.642	4.165	0.476
36.21	2	1.414	1.559	0.301	1.805	18.105	0.0276	-0.441	63.79	4.642	3.996	0.646
45.15	3	1.732	1.655	0.477	1.739	15.050	0.0221	-0.345	54.85	4.642	3.799	0.842
52.97	4	2.000	1.724	0.602	1.672	13.243	0.0189	-0.276	47.03	4.642	3.610	1.032
59.64	5	2.236	1.776	0.699	1.606	11.928	0.0168	-0.224	40.36	4.642	3.430	1.211
63.81	6	2.449	1.805	0.778	1.559	10.635	0.0157	-0.195	36.19	4.642	3.308	1.334
69.77	7	2.646	1.844	0.845	1.480	9.967	0.0143	-0.156	30.23	4.642	3.115	1.526
74.31	8	2.828	1.871	0.903	1.410	9.289	0.0135	-0.129	25.69	4.642	2.951	1.691
85.9	9	3.000	1.934	0.954	1.149	9.544	0.0116	-0.066	14.1	4.642	2.416	2.226
89.39	10	3.162	1.951	1.000	1.026	8.939	0.0112	-0.049	10.61	4.642	2.197	2.444
95.68	11	3.317	1.981	1.041	0.635	8.698	0.0105	-0.019	4.32	4.642	1.629	3.013
99.87	12	3.464	1.999	1.079	-0.886	8.323	0.0100	-0.001	0.13	4.642	0.507	4.135

CONCLUSION

Gastro retentive drug delivery system offer a valuable dosage form which delivers the drug at a controlled rate and specific site. The floating tablets of Imatinib Mesylate provide a better option for increasing the bioavailability for treatment of Leukemia by allowing a better control of fluctuations observed with conventional dosage form. Formulation IM4 appears suitable for further pre compression and Post compression parameters are with in the limits as per IP and In vitro drug release was 99.87 % for 12hrs.

REFERENCES

1. Leon Lachman, Herbert A. Liberman. the Theory and Practice of IndustrialPharmacy. 293-302.
2. Robinson Jr, Lee V.H.L, Controlled drug delivery. Fundamentals andApplications. 2nd edn. Marcel Dekker, New york: (1978); 24-36.
3. Brahmankar D.M, Jaiswal S.B. Biopharmaceutics and Pharmacokinetics atreatise. 1st ed. Vallabh prakashan; New Delhi: (1995); 64-70.
4. Chein Y.W. Novel Drug Delivery Systems. 2nd ed.: Marcel Dekker; NewYork: (1992); 4-56.
5. Ansel. Pharmaceutical Dosage form and Drug Delivery System, Lipincott,7th edition: 553.
6. Gennaro R.A. Remington.The Science and Practice of Pharmacy. 20th ed.New york : Lippincott Williams: (2000); 1045.
7. Banker G.S, Rhodes C.T. Modern Pharmaceutics. 3rd ed. Marcel Dekker,New York: (1996); 678-721.
8. Vyas S.P, Khar R.K. Controlled Drug Delivery: Concepts and Advances, 1sted. Vallabh prakashan, New Delhi: (2002); 345-376.
9. Friend DR. Oral delivery: A New approach to dosage forms. PharmaceuticalNews (2002); 9: 375-80.
10. Lalla JK. Introduction to controlled release and oral controlled drug deliverysystems. The Eastern Pharmacist (1991);45:25-28.
11. Hoffmann A.Pharmacodynamic aspects of sustained release preparations. Adv.Drug.Deliv.Rev. (1998);33:185-99.
12. Stanley SD, Lisbeth I.Drug delivery systems for challenging molecules.Int.J.Pharm. (1998);176:1-8.
13. P.G.Yeole. Floating Drug Delivery System: Need and Development. Int. J. Pharm Sci. (2005); 67(3): 265-272.
14. Shweta Arora. Floating Drug Delivery: A Review. AAPS Pharmscitech., (2005); 47(11): 268-272.
15. Libo Yang. A New Intragastric Delivery System for the Treatment of H.Pylori associated with gastric ulcers. Elsevier J. of controlled release. Apr(1999); 34 (5): 215-222.