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Research Article

DESIGN AND CHARACTERIZATION OF FLOATING CONTROLLED RELEASE TABLETS OF IMATINIB MESYLATE FOR SITE SPECIFIC DRUG DELIVERY

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ABSTRACT

Imatinib Mesylate is an anti cancer agent which is used to treat chronic myelogenous leukemia (CML), gastrointestinal stromal tumors (GISTs) and a number of other malignancies. In the present research work an attempt has been made for the formulation of floating tablet containing Imatinib Mesylate as a drug candidate which would remain in stomach or upper part of GIT for prolonged period of time thereby maximizing the drug release at the desired site within the stipulated time. In the present study Imatinib Mesylate floating tablets were prepared by wet granulation method. The floating tablets were subjected to preformulation studies, *in- vitro* drug release, kinetic studies and stability studies. FTIR studies shown there was no interaction between drug and polymers. The percentage of Imatinib Mesylate content from the tablets was determined by UV-Spectroscopy and ranged from 98.32±2.3 to 99.46±1.4. The *in-vitro* percentage release of Imatinib Mesylate from the optimized tablets at the end of 12 hours was 98.90±1.2. The kinetic studies revealed that the drug was released by zero-order kinetics. The optimized formulation was subjected to stability studies and shown there were no significant changes in drug content, physicochemical parameters and release pattern. From this study, it is concluded that, the formulations retained for longer period of time in the stomach and provides controlled release of the drug. Hence, it will be increasing the bioavailability of the drug and patient compliance.

Keywords: Imatinib Mesylate, floating tablet, prolonged period, wet granulation method.

INTRODUCTION

Oral drug delivery system represents one of the frontier areas of controlled drug delivery system; such dosage forms are having a major advantage is patient compliance. Floating drug delivery system belongs to oral controlled drug delivery system group that are capable of floating in the stomach by bypassing the gastric transit. These dosage forms are also defined as gas powered system (GPS), which can float in the contents of the stomach and release the drug in a controlled manner for prolonged periods of time. The release rate will be controlled depending upon the type and concentration of the polymer that swells, leads to diffusion and erosion of the drug[1].

The investigation was concerned with design and characterization of Imatinib Mesylate floating matrix tablets for controlled release in order to improve efficacy and better patient compliance. Imatinib Mesylate is an anti-cancer agent which is used to treat chronic myelogenous leukemia (CML), gastrointestinal stromal tumors (GISTs) and a number of other malignancies. It is the first member of a new class of agents that act by inhibiting particular tyrosine kinase enzymes, instead of non-specifically inhibiting rapidly dividing the cells. For the present study Imatinib Mesylate is selected as drug candidate, it fulfills the following characteristics which indicate its suitability for fabrication into the floating drug delivery system.

- Formulation of floating tablet containing Imatinib Mesylate as a drug candidate which would remain in stomach or upper part of GIT for prolonged period of time, there fore the maximum drug release is maintained at desired site. Because Imatinib Mesylate has good absorption in GIT.
- Imatinib Mesylate having low pKa which remain unionized in stomach for better absorption.
- Imatinib Mesylate is a site specific drug.
- To reduce the dose related side effects which are caused by Imatinib Mesylate long term therapy, and as well as to reduce total dose amount of the drug in the formulation[2].

By considering the above facts, Imatinib Mesylate floating matrix tablets were designed and characterized for controlled release in order to improve the patient compliance. Hence, the Imatinib Mesylate floating matrix tablets were prepared by wet granulation method using the different concentration of polymers.

MATERIALS AND METHODS

Materials

Imatinib Mesylate is obtained as gift sample from Celon labs pvt. Ltd.,Hyd. HPMCK4M, carbopol was obtained as gift sample from Lupin Laboratories, Pune. $NaHco_3$ was obtained from Fisher Sceintifics, Pvt ltd. Lactose was obtained as gift sample from Dr. Reddy's labs India ltd, Hyd. All other materials used were of analytical grade.

Experimental Methods

Pre formulation study

Almost all the drugs which are active orally are marketed as tablets , capsules or both. Prior to development of dosage forms with a new drug candidate, it is essential that certain fundamental physical and chemical properties of the drug molecule and other derived properties of the drug powder are determined. This information will dictate many of the subsequent events and possible approaches in formulation development.

Solubility study

The solubility study was used to identify the suitable solvent that possess good solubilizing capacity for Imatinib Mesylate. Solubility of Imatinib Mesylate in various solvents was determined by adding excess of Imatinib Mesylate in each selected solvents in each conical flask containing 20ml and is shaken for 24h using Rotary shaking apparatus. Then the solubility of drug in each solvent is observed visually and by UV spectrophotometrically at maximum wavelength 236 nm after relevant dilutions[3].

Excipients compatibility study

The successful formulation of a suitable and effective solid dosage form depends upon the careful selection of the excipients. Excipients are added to facilitate administration,promote the consistent release and bio availability of drug. It's necessary to study the compatibility of excipients with drug. Here IR spectroscopy was used to investigate and predict any physicochemical interaction between components in a formulation and to the selection of suitable compatible excepients.

Infrared spectrophotometer (IR)

Infrared (IR) spectroscopy was conducted and the spectrum was recorded in the wavelength region of 4000 to 400cm^{-1}. The procedure consisted of, dispersing a sample (drug alone, polymers alone and mixture of drug and polymers in KBr and compressing into discs by applying a pressure of 7 tons for 5 min in a KBr press. The pellet was placed in the light path and the spectrum was obtained[4,5].

Preparation of floating matrix tablets of Imatinib Mesylate[6]

Formulation development study was carried out for the preparation of floating tablet by using wet granulation method. Total weight of each floating matrix tablet is 400 mg. Imatinib Mesylate and all the ingredients are accurately weighed and passed through sieve # 60. Imatinib Mesylate is well mixed **(as shown in Table 1)** with half quantity of lactose, polymer and then mixed with remaining ingredients in geometric proportions. Mixed homogeneously in a polybag for about 5 -10 min. The obtained homogenous powder was taken in a glass mortar and granules were prepared by using isopropyl alcohol as granulating agent. The wet mass was passed through sieve # 14 and dried in hot air oven at a temperature of 50 ^{0}C, dried granules were sieved through sieve # 16. Then the obtained dry granules are lubricated with the previously weighed and sieved magnesium state, talc and aerosil to obtain the blend for compression.Then the lubricated blend is subjected to compression by 12 mm circular standard flat faced punch (Rimek mini press, model RSB-4, M/S: Karnavathi engineering, Ahmadabad)**.**

Evaluation of dry granule characteristics[7]

Imatinib Mesylate dry granules of different formulas from F1to F13 were evaluated for angle of repose, bulk density, tapped density, Hausner ratio, carr's index.

Angle of repose

The fixed funnel and free standing cone methods employ a funnel that is secured with its tip at a given height, h, which was kept 2cm above graph paper that is placed on a flat horizontal surface. With r being the radius, of base of conical pile, angle of repose can be determined by following equation: $\theta = \tan^{-1} (h/r)$

Where, θ is the angle of repose,

h is height of pile, r is radius of base of the pile

Bulk density and tapped density:

Both loose bulk density and tapped bulk density were determined. A quantity of 2gm of granules from each formula, previously light Shaken for the break of any agglomerates formed, was introduced into the 10ml of measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall down its own weight from the hard surface from a height of 2.5cm at 2 sec Intervals. The tapping was continued until no further change in the volume was noted

LBD and TBD were calculated using the following formulas:

LBD: Weight of the powder/volume of the packing.

TBD: Weight of the powder/Tapped volume of the packing.

Compressibility index

The compressibility index of the granules was determined by Carr's Compressibility index.

Carr's index (%) = [(TBD-LBD) * 100] / TBD

Where,

LBD: Weight of the powder/volume of the packing.

TBD: Weight of the powder/Tapped volume of the packing.

Hausner's ratio

Hausner's ratio can be determined by the following equation,

Hausner's ratio = TBD / LBD

Where, TBD -Tapped bulk densities & LBD- Loose bulk densities

Evaluation of tablet characteristics

Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations. Following parameters were evaluated

Weight variation[8]

Twenty (20) tablets from each batch were individually weighed in grams (gm) on an analytical balance. The average weight and standard deviation were calculated and the results were expressed as compliance or non-compliance of set limits.

Weight variation tolerance

Average weight (mg)	% Deviation allowed
130 or less	10
130-323	7.5
More than 324	5

Tablet hardness[9]

Tablet hardness was measured using a Monsanto hardness tester. The crushing strength of the 10 tablets with known weight and thickness of each was recorded in kg/cm^2 and the average hardness and standard deviation was reported.

Friability[9]

Twenty (20) tablets were selected from each batch and weighed. Each group of tablets was rotated at 25 rpm for 4 minutes (100 rotations) in the Roche friabilator. The tablets were then dusted and re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original tablets and % friability was calculated using formula.

$F= [1-W_0/W] \times 100$

Where,

W_0- Weight of tablet before test ,

W- Weight of tablet after test

Content uniformity[10]

From each batch of prepared tablets, ten tablets were collected randomly and powdered. A quantity of powder equivalent to weight of one tablet was transferred in to a 100 ml volumetric flask, to this 100 ml of 0.1N HCL was added and then the solution was subjected to sonication for about 2 hours. The solution was made up to the mark with 0.1N HCL. The solution was filtered and suitable dilutions were prepared with 0.1N HCL. Same concentration of the standard solution was also prepared. The drug content was estimated by recording the absorbance at 236 nm by using UV-Visible spectrophotometer.

Buoyancy / Floating Test[11]

The *in vitro* buoyancy was determined by floating lag time, as per the method described by a Rosa et al., 1994. Here, the tablets were placed in a 100-ml, beaker containing 0.1N HCL. The time required for the tablet to rise to the surface and float was determined as floating lag time and total

duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

Water uptake studies[6]

The swelling behavior of dosage unit can be measured either by studying its dimensional changes, weight gain or water uptake. The water uptake study of the dosage form was conducted by using USP dissolution apparatus-II in a 900ml of distilled water which was maintained at $37^o \pm 0.5^o$c, rotated at 50 rpm. At selected regular intervals the tablet was withdrawn and weighed. Percentage swelling of the tablet was expressed as percentage water uptake (%WU).

%WU = (Wt - Wo) * 100 / Wo

Where , Wt is the weight of the swollen tablet , Wo is the initial weight of the tablet.

Dissolution Study of tablets[10]

The tablet was placed inside the dissolution vessel. 5ml of sample were withdrawn at time intervals of 30, 60, 120 and 180, 240, 300, 360, 420, 480, 540,600, 660, and 720minutes. The volume of dissolution fluid adjusted to 900 ml by replacing 5ml of dissolution medium after each sampling. The release studies were conducted with 3 tablets, & the mean values were plotted versus time. Each sample was analyzed at 236 nm using double beam UV and Visible Spectrophotometer against reagent blank. The drug concentration was calculated using standard calibration curve Pure drug (IM) and marketed formulation (FM) dissolution studies also performed in the same manner but the time intervals for these formulations were every 5 minutes. That means for Imatinib Mesylate pure drug dissolution study performed up to 30 minutes and the time intervals was 5, 10,15,20,25 and 30 minutes. And for the marketed formulation dissolution study performed up to 60 minutes and time intervals was 5,10,15,20,25,30,35,40,45,50,55 and 60.

Kinetics of in-vitro drug release[12-14]

To study the release kinetics in-vitro release data was applied to kinetic models such as zero-order, first order, Higuchi and Korsemeyer-Peppas.

Zero-order,

$C = K_o t$ (1)

expressed in units of concentration/time, K_o is zero order release constant and t is the time in hrs.

First-order,

$\text{Log } C = \log C_o - Kt / 2.303$ (2)

Where C is the concentration, C_o is the initial concentration of drug, K is the first-order rate constant, and t is the time.

Higuchi,

$Q_t = K_H \cdot t^{1/2}$ (3)

Where Q_t is the amount of release drug in time t, K is the kinetic constant and t is the time in hrs.

Korsmeyer peppas,

$Mt / M_\infty = K \cdot t^n$ (4)

Where Mt represents amount of the released drug at time t, M is the overall amount of the drug (Whole dose). The value of n indicates the drug release mechanism related to the geometrical shape of the delivery system, if the exponent n = 0.5, then the drug release mechanism is Fickanian diffusion. If $n < 0.5$ the mechanism is quasi-Fickanian diffusion, and $0.5 < n < 0.5$, then it is non-Fickanian or anamolous diffusion and when n = 1.0 mechanism is non-Fickanian case II diffusion, $n > 1.0$ mechanism is non-Fickanian super case II.

Stability study[15]

In present study, stability studies were carried out at 40^0C and 75% RH for a specific time period up to 90 days for optimized formulation. For stability study, the tablets were sealed in aluminium packing coated inside with polyethylene. These sample containers were placed in desiccators maintained at 75%RH.

RESULTS AND DISCUSSION

Preformulation Studies:

Imatinib mesylate is very soluble in DMSO, 0.1 NHCL and it is also soluble in water due to its salt form.So, we select 0.1N HCL is solvent for further studies as it is acdic medium and its drug solubility **(as shown in Table 2 and represented in Figure 1).**

Drug- excipient interaction by using IR graphs

From below spectras, it was found that there is no significant change in plain drug spectra and drug with excepient spectras wavelengths **(as shown in Figure 2)**. So there is no Drug-Excipient interaction.

Micromeritic properties of Imatinib Mesylate and polymers

Micromeritic properties of pure drug and polymers indicating that the flow properties of drug and polymers were low **(as shown in Table 3)**. To increase the flow properties of drug and polymers granules were prepared by wet granulation method.

Granule properties of all batches

The granulation characteristics **(as shown in Table 4)**.are the most important interest to formulation scientist and therefore most universally measured. These basic measurements of the granulation have been used to develop and monitor the manufacture of many successful pharmaceutical dosage forms.

The bulk densities of granules were found to be between 0.432±0.08 to 0.469±0.06 g/cm^3. This indicates good packing capacity of granules. Carr's index evaluated interparticulate cohesive properties with angle of repose measurements and studied the effects of packing geometry of solids with bulk and tapped density. Bulk density and tapped density measurements found that density of a powder depends on particle packing and that density changes as the powder consolidates. Values of Carr's index below 15% usually show good flow characteristics, but readings above 25% indicate poor flowability. Carr's index was found to be between 9.8±0.08 to 15.6±0.06.

Hausners ratio is simple method to evaluate stability of powder column and to estimate flow properties. Low range was observed of Hausners ratio that indicates good flow ability. Many different types of angular properties have been employed to asses flow ability. Angle of repose is suited for particle > 150µm.Values of angle of repose $\leq 30^0$ generally indicate the free flowing material and angle of $\geq 40^0$ suggest a poor flowing material. The angle of repose is indicative of the flowability of the material. The angle of repose of all formulations fell within the range of 27.09±0.17 to 32.36±0.16 i.e. granules were of good flow properties.

Evaluation of Tablet characteristics

The floating tablets of Imatinib Mesylate were prepared by effervescent technique. The tablets were evaluated **(as shown in Table 5)** for weight variation, thickness, hardness, friability and drug content.

The total weight of each formulation was maintained constant; the weight variations of the tablets were within the permissible limits of 5%, as specified for tablet weighing more than 324mg. Weight of the tablet was fixed at 400mg and the weight variation for every batch was tested and found within the acceptance limits.

Hardness of the tablets of all batches was found to be between 6.1± 0.5 kg/cm^2 to 6.5±0.3 and was maintained for all the

batches in order to minimize the effect of hardness on the drug release because, the effect of polymer concentration is the only area of interest.

Tablet thickness was also used to assess the quality of tablets. Under uniform conditions of manufacture, the total weight of tablet and thickness were linearly related. The thickness of floating tablets ranged from 3.51±0.06 to 3.53±0.04 mm and linearly correlated with the weight of the tablets.

Friability test of all the formulations was found satisfactory showing enough resistance to the mechanical shock and abrasion. The values of friability are within the limit.

Drug content uniformity in all formulations was calculated and the percent of active ingredient ranged from 98.32±2.3 to 99.46±1.4 indicating good content uniformity in the prepared formulations as per within the limits as per IP. (Not less than 98% and not more than 102%).

Effect of Sodium bi carbonate concentration on floating lag time

Placebo tablets were prepared with changing the concentration of sodium bicarbonate concentration along with same concentration of drug and polymer. Finally, it can be concluded that the concentration of sodium bi carbonate increases the floating lag time decreased **(as shown in Table 6 and represented in Figure 3).**

Buoyancy determination

The formulated tablets on immersion in 0.1N Hydrochloric acid media they remain buoyant for 12 h with lag time of 90 to 263 seconds. Sodium bicarbonate was added as a gas-generating agent. The optimized concentration of effervescent mixture utilized aided in the buoyancy of all tablets. This may be due to the fact that effervescent mixture in tablets produced CO_2 that was trapped in swollen matrix, thus decreasing the density of the tablet below 1 making the tablets buoyant. All the batches showed good *in vitro* buoyancy but F4 formulation shows more floating lag time due to the high concentration of Carbopol 934P polymer (as shown in **Table 7 and represented in Figure 4)**

Water uptake studies

The swelling index was calculated with respect to time. As time increases, the swelling index was increased, because weight gain by tablet was increased proportionally with rate of hydration. Later on, it decreased gradually due to dissolution of outermost gelled layer of tablet in to dissolution medium **(as Shown in Table 8 and represented in Figure 5)**. The direct relation was observed between swelling index and polymer concentration.

In vitro dissolution testing

The in vitro dissolution testing was performed (as shown in **Table 9,10 and represented in Figure 6,7)** and the results of the formulations were expressed as mean ± S.D (n=3).

First the dissolution studies of pure Imatinib Mesylate (IM), marketed formulation CELONIB (100mg) (FM) were conducted, 0.1 N HCL used as dissolution medium. Imatinib Mesylate highly soluble in 0.1N HCL, so the complete drug release was observed within 10 minutes. In case of marketed formulation, it's a conventional dosage form that's why drastic drug release was takes place within 45 minutes. Because of this drastic release, dose releated side effects will occurred in long term therapy, the dosing frequency also high due to this, fluctuation in plasma concentration also takes place. To reduce these consequences controlled release Imatinib Mesylate floating matrix tablets were fabricated.

In vitro dissolution study of formulations F1 was done in 0.1 N HCL and the percent of drug release from formulation F1 and F2, was 98.06 in 6hr and, 99.76 in 10hr, these formulation is unable to sustain the drug release desired period of time. It is due to the hydrophilic nature of the polymer HPMC K4M, which is used in maximum concentration in this formulation. This formulation floated for 12 hr.

In vitro dissolution study of formulations F3, and F4 were done in 0.1 N HCL and the percent of drug release from formulations F3 and F4 was 98.48 in 12hr, 85.24 in 12 h respectively, in case of formulation F3, 98.48% of the drug was released in 12 h. The reason for this could be that the gel layer formed around the tablet was stronger, with few intestinal spaces between the micro gels. And this diffusion layer of Corbopol polymer retards the drug release from the formulation. Both these two formulations floated for 12 h. Formulation F4 was sustained for more than 12hr, and floated with a lag time 263 sec, due to the high concentration of Carbopol. When Carbopol concentration increased simultaneously adhesive nature of the polymer also increased, so it shows more floating lag time when compare with other formulations. Formulation F3 obtained the desired drug release profile and floated with a lag time of 98 sec, for these reasons, it was considered as optimized formulation.

In all formulations as the concentration of carbopol polymer increased the rate of drug release from the formulations was decreased.

Dissolution Profile Modeling

The mechanism of release for the all formulations was determined by finding the R^2 value for each kinetic model viz. Zero-order, First-order, Higuchi, and Korsmeyer-Peppas corresponding to the release data of formulations. For Imatinib Mesylate (IM) R^2 value of Higuchi model near to 1 and marketed formulation (FM) R^2 value of Higuchi and zero-order models are very near to 1 than the R^2 values of other kinetic models **(as shown in Table 11)**. Thus it can be said that the drug release follows Higuchi and zero-order model mechanism.

For all formulations F1 to F4, R^2 value of Zero order and Higuchi models are very near to 1 when compare with other models. And optimized formulation F3, R2 values of Zero order and Higuchi are 0.994, 0.988 respectively.

It can be concluded that all formulations F1 to F4 drug release patterns were following the Zero order and Higuchi release kinetic models. The n values of Korsmeyer-Peppas model of the all formulations are in between 0.118 to 0.488. Therefore the most probable mechanism that the release patterns of the formulations followed was Fickian diffusion.

Stability studies

Stability studies revealed that there was no significant change in the drug content, (98.85 ± 1.4%) the release rate of the drug (98.48 ±1.5 %) and buoyancy characters (Floating lag time of 60sec floating duration of >12 h) of the optimized formulation F3 kept on stability studies(40^0C/75% RH).

CONCLUSION

Imatinib Mesylate tablets can be formulated to increase the gastric residence time and thereby achieve the slow release of the drug in a constant manner. Formulation F3 gave better controlled drug release and floating properties in comparison to the other formulations. Formulation F3 contains combination of HPMC K4M & Carbopol polymers; it is better polymer combination to produce promising results in release profile. Formulated tablets showed satisfactory results for their evaluation like Hardness, weight variation, floating lag time, floating time, and in vitro drug release. Finally, it can be concluded that Imatinib Mesylate was good candidate

for the preparation of Floating drug delivery system due to it gastric stability, gastric absorption.

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Table 1: Composition of floating matrix tablet of Imatinib Mesylate

Formulation Code	Imatinib Mesylate (mg)	SBC (mg)	HPMC K4M (mg)	Carbopol (mg)	Lactose (mg)
F1	120	70	105	15	78
F2	120	70	90	30	78
F3	120	70	75	45	78
F4	120	70	60	60	78

SBC=Sodium bi carbonate, HPMC=Hydroxy propyl methyl cellulose,
All formulations contain 1% of Talc, 1% of Magnesium stearate and 1% of Aerosil.

Table 2: Solubility study of Imatinib Mesylate in different solvents

Solvent	Concentration(mg/ml)
DMSO	63.8
0.1N HCL	55.6
Water	52.7
Ethanol	7.8
n-Octanol	0.24
7.4 pH buffer	0.18
Acetone	0.14

Table 3: Micromeritic properties of Imatinib Mesylate and polymers

Material	Bulk density (gm/cc) ± SD, n=3	Tapped density (gm/cc) ± SD, n=3	Carr's index (%) ± SD, n=3	Hausner's ratio ± SD, n=3	Angle of repose (degree) ± SD, n=3
Imatinib Mesylate	0.233	0.352	33.8	1.51	36.72
HPMC K4M	0.341	0.557	39	1.63	41.28
Carbopol	2.10	1.76	19.3	0.83	28.7

Table 4: Granule properties of all batches

Bach Code	Bulk density (gm/cc) ± SD, n=3	Tapped density (gm/cc) ± SD, n=3	Carr's index (%) ± SD, n=3	Hausner's ratio ± SD, n=3	Angle of repose (degree) ± SD, n=3
F1	0.450±0.05	0.518±0.03	13.1±0.10	1.15±0.04	28.20±0.12
F2	0.449±0.02	0.532±0.07	15.6±0.06	1.18±0.03	28.98±0.14
F3	0.469±0.06	0.520±0.06	9.8±0.08	1.10±0.07	32.36±0.16
F4	0.432±0.08	0.510±0.03	15.5±0.06	1.18±0.09	27.32±0.17

All values are expressed average ± SD;(n=3)

Table 5: Physicochemical properties of all batches

Formula code	Weight variation(mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content(%)
F1	405±1.6	6.5±0.5	3.52±0.03	0.64±0.06	98.32±2.3
F2	404±1.4	6.5±0.3	3.51±0.06	0.84±0.03	98.99±1.6
F3	402±1.4	6.1±0.5	3.52±0.05	0.62±0.02	99.46±1.4
F4	405±1.3	6.4±0.4	3.53±0.04	0.67±0.05	98.46±1.2

All values are expressed average ± SD;(n=3)

Table 6: Effect of Sodium bi carbonate concentration on floating lag time

Sodium bi carbonate concentration (mg)	Floating lag time (seconds)
20	162
30	148
40	134
50	120
60	106
70	98

Table 7. Floating properties of Imatinib Mesylate tablets

Formulation code	Lag time(sec)	Total floating time(hr)
F1	92	>12
F2	92	>12
F3	98	>12
F4	263	>12

Table 8. Swelling index of formulations F1

Time(min)	F1	F2	F3	F4
60	116.2±1.4	123.4±1.5	132.1±1.4	148.2±1.6
120	186.5±1.7	135.7±1.6	145.3±1.8	156.8±1.5
180	235.4±1.4	148.6±1.7	156.5±1.4	167.7±1.6
240	294.3±1.1	163.2±1.5	172.3±1.8	186.2±1.4
300	263.4±1.6	179.4±1.8	195.4±1.6	198.5±1.6
360	236.9±1.5	196.3±1.4	205.6±1.7	212.8±1.3
420	217.8±1.8	218.5±1.6	218.6±1.6	224.5±1.5
480	197.3±1.6	242.2±1.2	228.4±1.5	236.9±1.6
540	154.5±1.4	236.4±1.3	235.1±1.4	241.9±1.4
600	128.6±1.8	221.1±1.5	253.3±1.7	258.7±1.8
660	107.2±1.6	193.1±1.4	223.2±1.8	269.5±1.4
720	86.8±1.6	156.2±1.6	195.7±1.4	244.1±1.7

Table 9: Cumulative % drug release of pure drug Imatinib Mesylate (IM) and marketed formulation (FM) CELONIB – 100mg

Time in minutes	% of drug release from pure drug Imatinib Mesylate (IM)	% of drug release from marketed formulation (FM) CELONIB – 100mg
0	0	0
5	78.5±1.2	12.4±1.7
10	99.4±1.6	28.9±1.3
15	99.6±1.8	37.5±1.7
20	99.6±1.4	49.4±1.5
25	99.8±1.7	58.6±1.6
30	99.8±1.5	66.2±1.4
35		79.1±1.5
40		86.3±1.7
45		98.5±1.8
50		99.8±1.7
55		99.8±1.6
60		99.8±1.4

All values are expressed average ± SD;(n=3)

Table 10: Cumulative % drug release of formulation from Formulations F1-F8

Sampling time (min)	F1	F2	F3	F4
0	0	0	0	0
30	25.29±1.5	08.78 ±1.1	03.22 ±1.1	01.51±1.1
60	36.40±1.4	17.60±1.3	10.63±1.0	07.63±1.3
120	49.93±1.2	30.28 ±1.2	20.31±1.2	13.47±1.1
180	63.31 ±1.3	38.96±1.6	30.99±1.2	19.88±1.4
240	75.70±1.5	49.07±1.4	39.25±1.4	28.50 ±1.2
300	84.53±1.2	58.61±1.3	45.93±1.2	32.27±1.1
360	98.06±1.4	66.30 ±1.1	55.34±1.4	41.38±1.3
420		75.98±1.3	63.03±1.1	47.51±1.1
480		86.09±1.5	70.29±1.3	55.34±1.4
540		91.65±1.3	78.55±1.5	60.89±1.3
600		99.76±1.4	85.95±1.4	70.29±1.2
660			91.79±1.4	77.69±1.4
720			98.90±1.2	85.24±1.3

All values are expressed average ± SD;(n=3)

Table 11. Regression coefficient (R^2) values for different kinetic models for all formulations

Formulation	Zero order	First order	Higuchi	Korsmeyer&Peppas	Peppas(n)
F1	0.762	0.704	0.875	0.227	0.118
F2	0.968	0.873	0.985	0.161	0.251
F3	0.994	0.760	0.988	0.348	0.488
F4	0.985	0.917	0.995	0.081	0.261

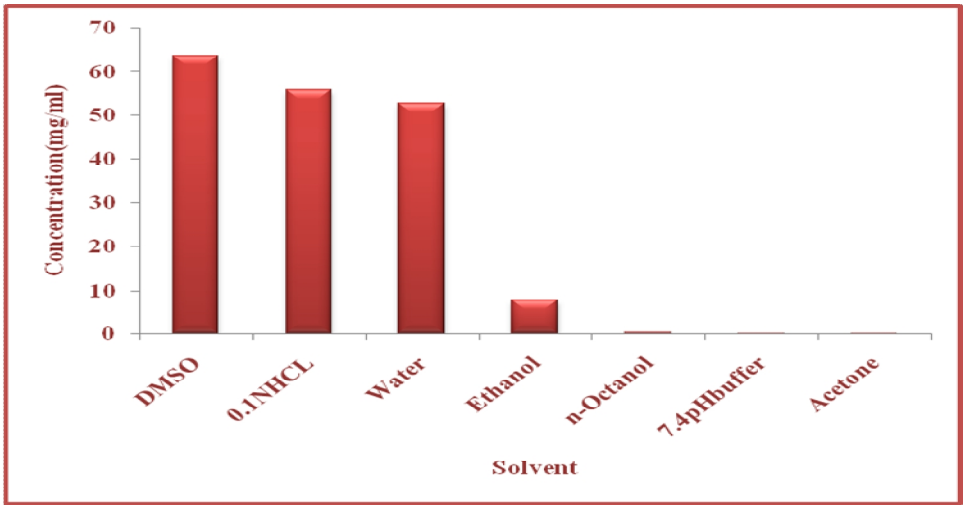

Fig 1: Solubility of Imatinib Mesylate in different solvents

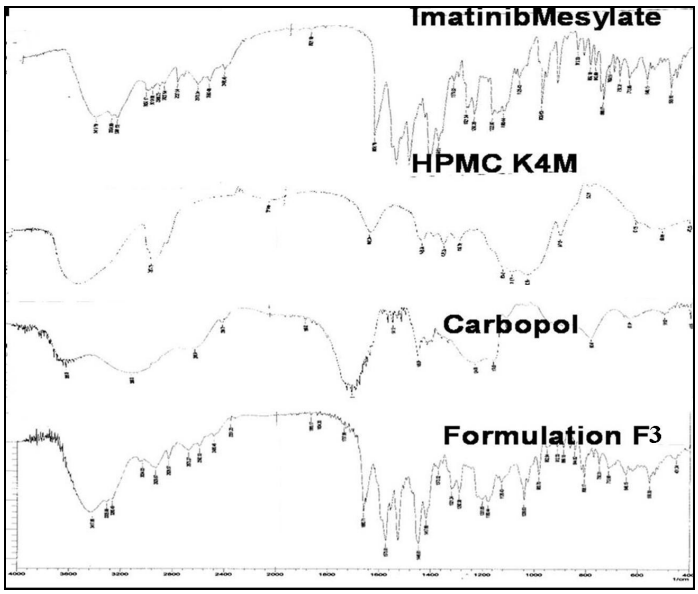

Fig 2: FTIR Spectra Of a) Imatinib Mesylate b) HPMC K4M c) Carbopol d) Formulation F3.

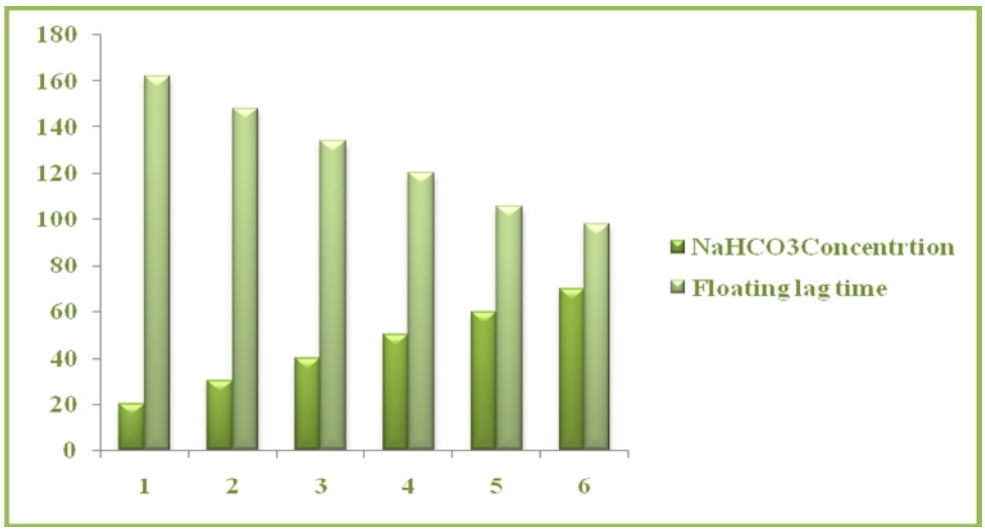

Fig 3: Graphical representation of Sodium bi carbonate Concentration on floating lag time

After 60 seconds

After 90 seconds

After 6 hours

Fig 4: In vitro buoyancy study of Imatinib Mesylate floating matrix tablets

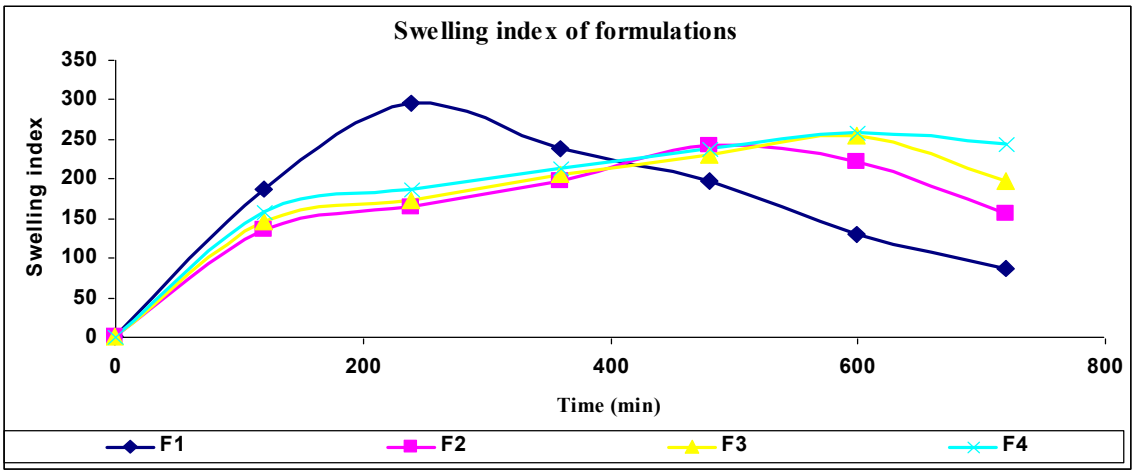

Fig 5.Swelling index of formulations F1-F4

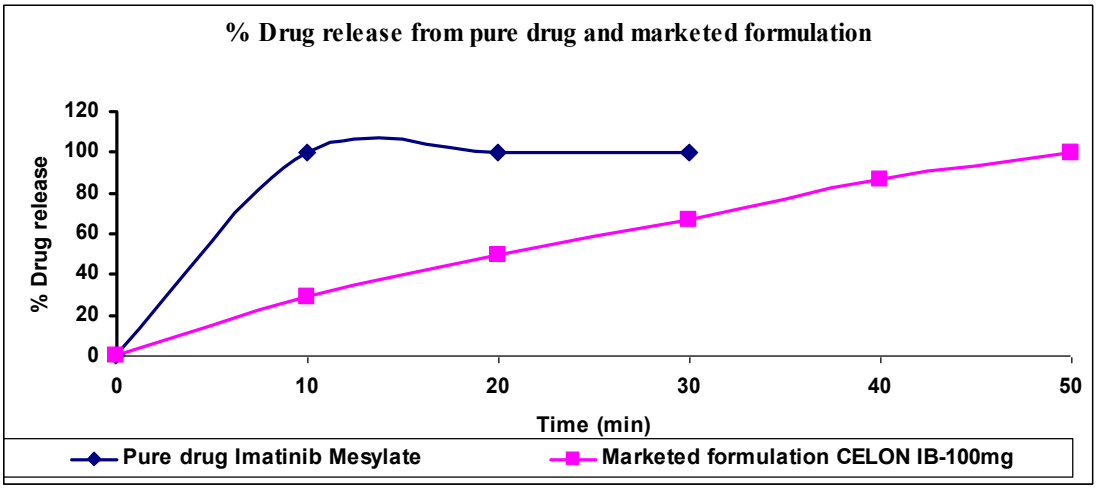

Fig 6.Cumulative % drug release of pure drug and marketed formulation

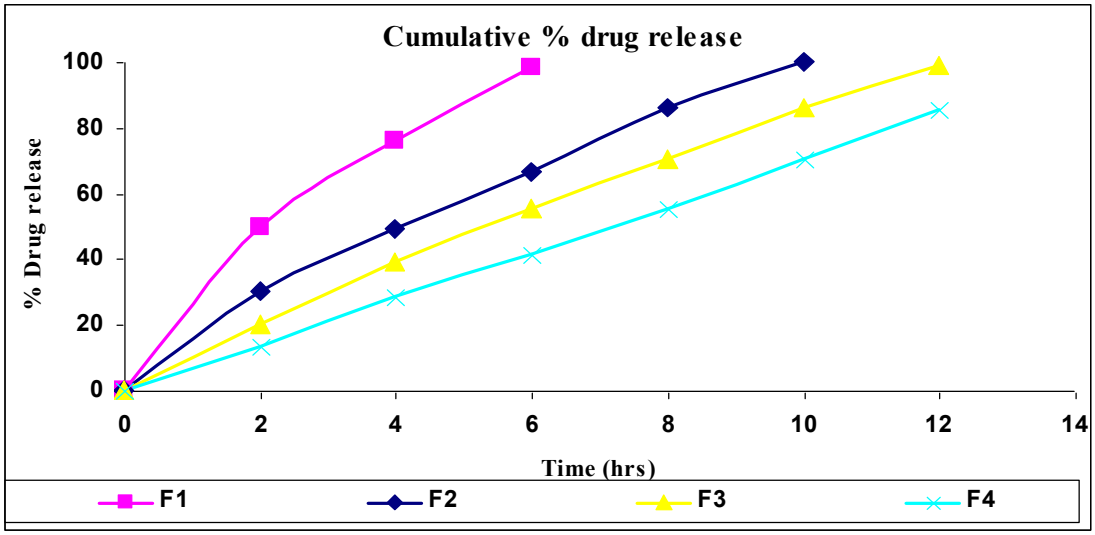

Fig 7. Cumulative % drug release from Formulations F1-F4

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