ISSN: 0976-3031

Available Online at http://www.recentscientific.com

CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 10, Issue, 07(A), pp. 33323-33328, July, 2019

International Journal of Recent Scientific Research

DOI: 10.24327/IJRSR

Research Article

FORMULATION AND EVALUATION OF FLOATING IN-SITU GEL OF IMATINIB

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DOI: http://dx.doi.org/10.24327/ijrsr.2019.1007.3649

ARTICLE INFO

Article History:
Received 4th April, 2019
Received in revised form 25th May, 2019
Accepted 23rd June, 2019
Published online 28th July, 2019

Key Words:

Imatinib, HPMC, Sodium alginate, Calcium Carbonate, floating in situ gels.

ABSTRACT

The characterization peaks of Imatinib mesylate were found in formulation undisturbed indicates the compatibility of the drug used with the excipients of the formulation.The monograph of Imatinib mesylate has melting point range of 214-224°C. The sample of Imatinib mesylate obtained from Dr. MACS Bio Pharma Pvt Ltd, Hyderabad. Indicating the purity of the drug sample. Clarity of all the formulations was found to be satisfactory. The pH of all formulations was found to be satisfactory and lies in the range 7.03±0.1 to 7.54±0.2. The drug content uniformity data has shown that all the formulations were found to be uniform in drug content in the range of 95.05-99.25%. Gelation study was performed to explain gelling capacity. Gelling capacity of all formulations were designated as + (gel formation takes after few minutes and disperse rapidly), ++(immediate gel formation, remains un-dispersed for few hours) and +++ (immediate gel formation, the gel was remains for extend time). The results of rheological study of prepared in situ gel confirms as the viscosity decreases with increase in angular velocity. Results indicated that all formulations are having an optimum viscosity and all formulations were pourable at normal conditions. The drug release data obtained for all the formulations were shown in fig 4.5. The cumulative percent drugrelease of formulation was 99.25±3.5 for formulation 1, For formulations F2 to F6 the values 98.25±2.5, 95.05±2.5, 96.32±1.3, 95.27±0.2 and 98.24±1.5respectively till 12th hour. From the result of drug content, gelation pH, drug content, and drug release studies for all formulation, F6 formulation was selected as best formulation which has shown highest drug release till 12thhour. Hence F6formulation was chosen for stability studies.

INTRODUCTION

Controlled release (CR) dosage forms have been extensively used to improve therapy with several important drugs. , incorporation of the drug in a controlled release gastro retentive forms (CR-GRDF) which can remain in the gastric region for several hours would significantly prolong the gastric residence time of drugs and improve bioavailability, reduce drug waste, and enhance the solubility of drugs that are less soluble in high pH environment.

Floating drug Delivery Systems

Floating drug delivery systems have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time while the system is floating on the gastric contents the drug is released slowly at the desired rate from the system. This results in increased GRT and better control of fluctuations in plasma drug concentration.

Single unit floating drug delivery system

a. Non-effervescent systems: by using colloidal gel barrier system and microporous compartment system.
b. Effervescent systems: by using volatile liquid containing systems and gas generating system.

Multiple unit floating drug delivery system

a. Non-effervescent systems: by using the alginate beads and hallow microspheres.
b. Gas generating systems.
c. Ion-exchange resin system.
d. Bio/muco adhesive systems.
e. Swelling systems.

MATERIALS AND METHODS

Preparation

Imatinib mesylate was obtained from Dr.MACS Biopharma, Hyderabad, as a gift sample. Different formulations of Imatinib mesylate in situ hydrogel were prepared as per the Table 1.

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Sodium alginate solutions at different concentrations were prepared in half volume of deionized water containing calcium chloride (0.1% w/v) and sodium citrate (0.5% w/v). This solution was heated to 60°C with stirring. After cooling below 40°C; another one-third quantity of deionized water containing HPMC K100M (viscosifying agent) was added with continuous stirring. Further, Imatinib mesylate, calcium carbonate and sodium citrate were added to above mixture, and final volume was made up to 20 ml with deionized water. The ingredients used in the preparation of formulations were shown in table

Table 1 Formulations used in the study

Name of the ingredient	Formulations(mg)					
	F1	F2	F3	F4	F4	F6
Imatinib mesylate	400	400	400	400	400	400
Sodium Alginate	1000	1000	1500	1500	2000	2000
Sodium citrate	500	500	500	500	500	500
Calcium carbonate	250	500	250	500	250	500
HPMC	600	600	600	600	600	600
Distilled water (ml)	100	100	100	100	100	100

Preformulation Studies

Preformulation may be described as a stage of development during which the physicochemical and biopharmaceutical properties of a drug substance are characterized. It is important part of the drug development processInfra-red spectroscopy is widely used in pharmaceutical research. IR spectroscopy is routinely used for compound identification as a fingerprinting tool. IR spectroscopy also has its application in studies of drug-excipient interaction, contaminant analysis etc.IR spectrum with high quality is acquired with KBr pellet method. Compatibility study of drug with the excipients was determined by using FTIR. The sample powder of drugs, excipients and mixture of both were subjected to FTIR study. The mixture spectra were compared with that of the original spectra.

Standard Curve of Imatinib Mesylate

Preparation of 0.1N Hydrochloric acid

8.5 ml of concentrated hydrochloric acid was diluted with distilled water and the volume was made upto 1000ml with distilled water.

Preparation of Imatinib mesylate Standard Stock Solution in 0.1N HCl

A Standard Solution of Imatinib mesylate was prepared by dissolving accurately weighed 100 mg of Imatinib mesylate with little quantity of 0.1N HCl solution, in a 100 ml volumetric flask. The volume was made up to 100 ml with 0.1N HCl, to obtain a stock solution of 1000µg/ml. From the above solution several dilutions are made to obtain 50, 75, 100, 125, 150 µg/ml solutions. The absorbencies of these drug solutions were estimated at λ_{max} 236 nm.

Post formulary Evaluation

The prepared formulations were evaluated for following parameters.

Physical Appearance and clarity

The developed formulations were inspected visually for clarity in sol and gel form by visual observation in presence of highly illuminated light against a black and white background clarity test apparatus.

pH: The pH of the developed formulations was determined using digital pH meter.

Drug content Uniformity

Each formulated gel (600 mg) was dissolved in 100 ml of 0.1N HCl. The solution was filtered through a cellulose acetate membrane (0.45 µm) and the drug content was determined by UV spectroscopy at a wavelength of 237 nm after suitable dilution with 0.1 N of HCl.

In vitro Gelation Studies

The gelling capacity was determined by taking one drop of the preparation in a test tube containing 2 ml of freshly prepared 0.1M HCl at 37±0.5^{o} C and time taken to form gel and the gel to get dissolved was noted.

Rheological Studies

The study was performed using Brookfield viscometer. Angular velocity was increased gradually from 0.5 to 60 rpm using spindle No. 63. The hierarchy of angular velocity was reversed and the average dial readings were considered to calculate the viscosity. Then the prepared solutions were allowed to gel in 0.1M HCl and then again the viscosity determination was carried out. The temperature was maintained within 37±0.5°C.

In Vitro Floating Study

The in vitro floating study was determined with minor modification of the method by using USP dissolution apparatus II (ERWEKA DT 600HH, Germany) having 500 ml of simulated gastric fluid (0.1 N HCl) maintained at 37±0.5^{0}C with a paddle speed of 50 rpm. 10 ml of the prepared in situ gelling formulations were withdrawn with disposable syringe (with removed tip) and added into the dissolution vessel containing simulated gastric fluid. The time the formulation took to emerge on the medium surface (floating lag time) and the time the formulation constantly floated on the dissolution medium surface (duration of floating) were recorded.

Floating lag time

The FLT is defined as the time taken by the gel to reach the top from the bottom of the dissolution flask. The FLT of gel was determined by visual inspection using a USP (Type II) dissolution test apparatus containing 900 ml of 0.1N HCl at 37± 0.5°C.

Floating Duration

The duration of time for which the formulation floats constantly on the surface of the medium is known as the duration of floating. The duration of floating of gels was determined using a dissolution test apparatus USP (Type II) containing 900 ml of 0.1N HCl at 50 rpm at 37°C ± 0.5°C.

Gel Strength

The gel strength apparatus was fabricated in house using a measuring cylinder of 1.2 cm radius and a bore of 0.1 mm at its

base. A needle 2 cm in length was used to which a nylon thread was tied. Test formulation (10 ml) was taken in the cylinder with temporarily sealed bore followed by addition of 50 ml 0.1N HCl for gelation. After gelation, the HCl was drained off by opening bore seal leaving the gel mass formed. The needle was made to rest on to surface of the gel. At the free end of the thread a light weight pan was attached to which the weights were added. The gel strength was reported in terms of weight required to pass the needle probe through the formed gel mass. The gel strength is calculated using this formula:

Gel strength = Mg/a

Where,

M = Weight at which the pass the needle probe through formed gel mass
g = Gravitational force, and
a = Area of surfaces

Measurement of Drug Release rate from gels

The in vitro release of Imatinib mesylate from the gels was measured by using modified USP- II dissolution test apparatus stirrer at 50 rpm. The dissolution medium used was 500 ml of 0.01N HCl and temperature was maintained at 37±0.5°C. 10 ml formulation was drawn up using disposable syringe, the needle was wiped clean and excess formulation was removed from the needle end. 10 ml of in situ gel solution was placed into Petri dish and Petri dish containing formulation was kept in the dissolution vessel containing dissolution medium. At every time interval, a precisely measured sample of the dissolution medium was removed and replenished with pre-warmed (37±0.5°C) fresh medium. The amount of Imatinib mesylate in each sample was determined by double beam UV Spectrophotometer (Shimadzu Co Ltd, Japan).

Accelerated Stabilities Studies

The best formulation was subjected to stability studies at humidity condition at 75±5%,ambient temperature 40±2°C for a period of three months. The samples were collected at periodicinterval of 0 days, 30 days, 60 days and 90 days and were evaluated for appearance, content uniformityand in vitro drug release studies.

Table 2 Melting Point of Imatinib Mesylate

Trials	Melting Point (^{O} C)
1	219.00
2	222.00
3	220.00
Average	**220.3±1.52**

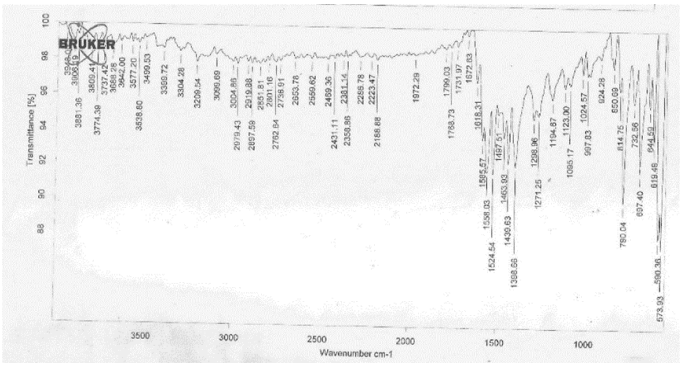


Fig 1 FT-IR spectrum of imatinib pure drug

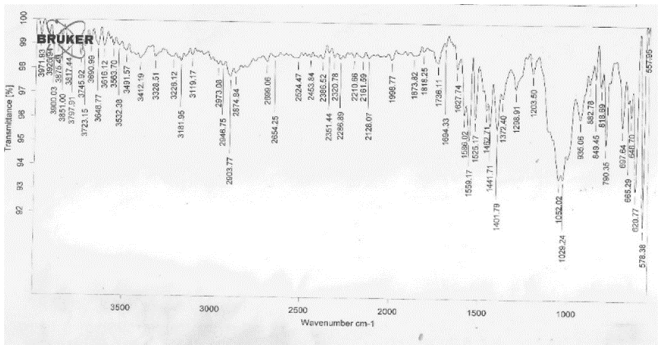
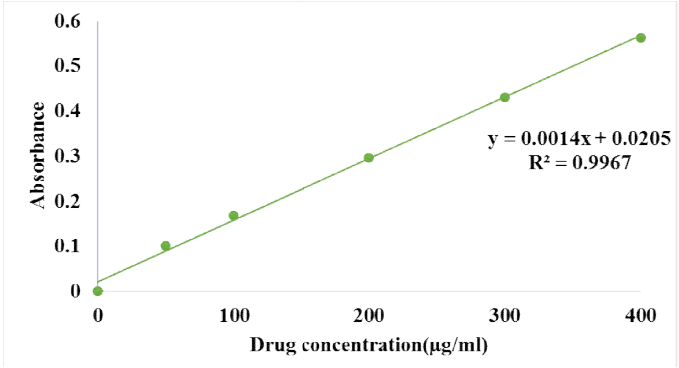


Fig 2 FT-IR spectrum of imatinib and excipient blend

Standard Calibration curve of Imatinib Mesylate

Table 3 Absorbance of Imatinib with different concentrations at 235 nm

Concentration (µg/ml)	Absorbance
0	0.000±0.00
50	0.102±0.01
100	0.169±0.01
200	0.296±0.01
300	0.431±0.01
400	0.564±0.02
All values mentioned as mean±SD; Number of trials (N)=3	



Graph 1 Standard calibration curve of Imatinib Mesylate

Physical Appearance and clarity

The prepared gels were in clear and pale yellow in colour.

pH

The prepared gels pH was nearer to neutral and ranged from 7.03±0.1 to 7.54±0.2 .

Drug content Uniformity

The prepared in situ gel found to have uniformity in drug content and ranged from 95.05±2.5-99.25±3.5% .

In vitro Gelation Studies

Depend on time required for gelation and time of its retention as gel, the prepared in situ gels were categorized as +, ++ and +++. These were showed in the table 4.

Rheological Studies

The angular velocity and viscosity before and after gelation was tabulated in Tables, the corresponding rheograms.

In Vitro Floating Study

Time taken by the formulation for Floating and sustaining on surface of water was determined and shown in table

Table 4 *In vitro* gelling capacity

Formulation	Viscosity (cps)	Gelling Capacity	pH	Floating lag time (sec)	Floating time (h)	Drug content (%)
F1	800±2.15	+	7.54±0.2	59±1	=10	99.25±3.5
F2	850±3.26	++	7.39±0.1	59±3	>12	98.25±2.5
F3	900±2.54	+++	7.23±0.2	63±2	>12	95.05±2.5
F4	1200±1.25	+++	7.22±0.1	48±3	>12	96.32±1.3
F5	1050±1.84	++	7.03±0.1	75±5	>12	95.27±0.2
F6	1150±2.80	+++	7.27±0.3	51±1	>12	98.24±1.5

All values mentioned as mean±SD; Number of trials (N)=3; +Gel after few minutes, dissolved rapidly; ++Gelation immediately, remains for few hours; +++Gelation immediately, remains for extended period.

Table 5 Determination of Viscosity before gelation

RPM	Formulations (before gelation)					
	F1	F2	F3	F4	F5	F6
10	100±1.2	96±2.5	95±3.5	98±6.2	97±1.2	92±5.2
20	65±2.5	62±2.6	71±1.2	70±2.5	66±3.5	69±0.2
30	62±1.6	60±3.5	62±1.2	65±1.2	56±1.5	55±0.2
40	52±3.5	52±2.8	55±1.2	62±3.2	45±0.3	51±1.2
50	48±2.5	45±2.4	45±0.1	55±1.1	32±0.6	48±0.6
60	35±1.6	32±1.7	32±1.2	51±1.2	25±0.5	35±0.8

All values mentioned as mean±SD; Number of trials (N)=3

Table 6 Determination of Viscosity after gelation

RPM	Formulations (before gelation)					
	F1	F2	F3	F4	F5	F6
10	100±1.2	96±2.5	95±3.5	98±6.2	97±1.2	92±5.2
20	65±2.5	62±2.6	71±1.2	70±2.5	66±3.5	69±0.2
30	62±1.6	60±3.5	62±1.2	65±1.2	56±1.5	55±0.2
40	52±3.5	52±2.8	55±1.2	62±3.2	45±0.3	51±1.2
50	48±2.5	45±2.4	45±0.1	55±1.1	32±0.6	48±0.6
60	35±1.6	32±1.7	32±1.2	51±1.2	25±0.5	35±0.8

All values mentioned as mean±SD; Number of trials (N)=3

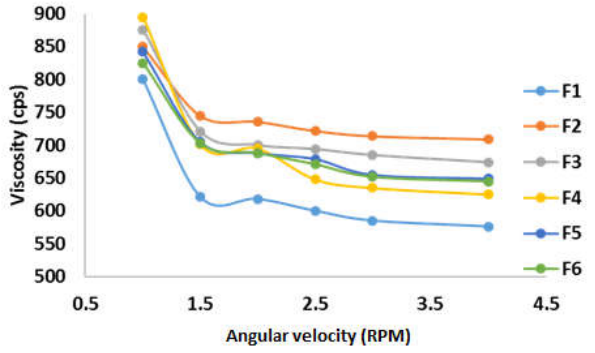


Fig 3 Viscosity of formulation before gelatin

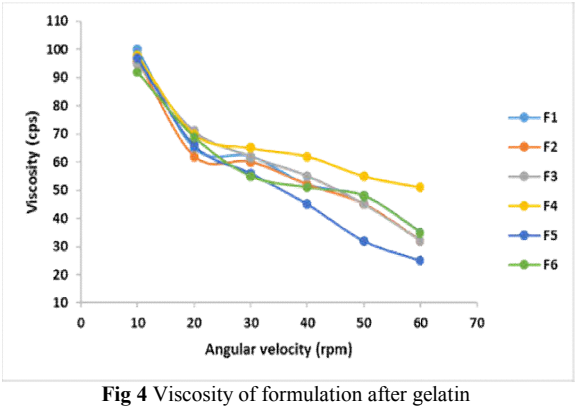


Fig 4 Viscosity of formulation after gelatin

Table 7 *In vitro* drug dissolution profile of prepared formulations

Time (h)	Formulations					
	F1	F2	F3	F4	F5	F6
0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
0.5	23.53±0.2	22.15±0.2	16.61±0.3	19.01±0.2	17.53±0.2	18.92±0.6
1	34.70±1.2	31.68±0.8	22.60±0.2	38.02±0.3	24.46±0.3	25.86±1.2
2	42.55±1.2	40.67±0.9	27.83±1.2	42.01±0.6	29.47±1.2	30.64±0.2
3	49.51±0.5	47.16±1.3	31.23±3.0	45.02±1.2	33.57±1.2	34.99±2.5
4	56.05±0.6	55.07±0.5	35.57±1.3	50.03±1.3	37.24±1.3	45.02±1.2
5	65.87±1.2	64.19±0.3	40.41±0.3	59.05±0.6	42.31±1.2	56.03±1.3
6	77.13±1.5	75.21±1.2	44.11±0.2	65.09±0.3	47.65±1.3	59.08±1.2
7	86.37±1.5	83.68±2.5	49.22±1.2	67.05±0.2	53.24±0.5	63.01±0.2
8	92.00±0.2	91.39±1.6	55.29±2.3	70.05±3.2	60.49±0.3	66.18±0.6
9	95.01±0.5	95.02±1.5	61.39±3.2	75.06±2.0	67.31±1.2	70.02±0.3
10	98.02±0.3	96.02±1.3	68.45±2.2	80.03±1.2	74.64±1.2	72.05±0.5
11	99.05±0.2	97.09±1.2	76.47±1.2	85.96±1.5	82.69±0.3	75.02±0.3
12	99.02±0.6	99.39±1.2	88.03±2.3	93.63±1.2	92.19±1.2	79.03±0.9

All values mentioned as mean±SD; Number of trials (N)=3

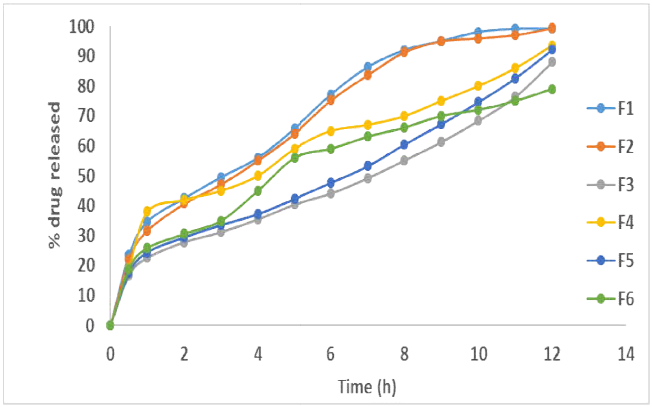


Fig 5 *In vitro* drug dissolution profile of prepared formulations

Accelerated Stability Studies

The optimized formulation shown the following characteristics before and after accelerated stability studies.

Table 8 The parameters before and after stability studies

Stability studies	Parameters					
	Viscosity (cps)	Gelling Capacity	pH	Floating lag time (sec)	Floating time (h)	Drug content (%)
Before	1150±2.80	+++	7.27±0.3	51±1	>12	98.24±1.5
After	1150±3.10	+++	7.27±0.3	51±1	>12	98.20±1.1

All values mentioned as mean±SD; Number of trials (N)=3; +Gel after few minutes, dissolved rapidly; ++Gelation immediately, remains for few hours; +++Gelation immediately, remains for extended period.

DISCUSSION OF RESULTS

The characterization peaks of Imatinib mesylate were found in formulation undisturbed indicates the compatibility of the drug used with the excipients of the formulation.

Melting Point

The monograph of Imatinib mesylate has melting point range of 214-224°C. The sample of Imatinib mesylate obtained from Dr. MACS Bio Pharma Pvt Ltd, Hyderabad, shown melting point at 220.3±1.52°C. Indicating the purity of the drug sample.

Appearance: Clarity of all the formulations was found to be satisfactory.

pH: The pH of all formulations was found to be satisfactory and lies in the range 7.03±0.1 to 7.54±0.2.

Drug content: The drug content uniformity data has shown that all the formulations were found to be uniform in drug content in the range of 95.05-99.25%.

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Rheological studies: The results of rheological study of prepared in situ gel confirms as the viscosity decreases with increase in angular velocity. Results indicated that all formulations are having an optimum viscosity and all formulations were pourable at normal conditions.

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