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Research Article

FORMULATION AND IN VITRO EVALUATION OF DASATINIB FLOATING MICROSPHERES

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ABSTRACT:
Dasatinib is a tyrosine kinase inhibitor used for the treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia or chronic myeloid leukemia. The present work is formulation of Dasatinib floating microspheres by using xanthan gum, Eudragit S100 and Ethyl Cellulose. All the formulations were subjected for preformulation evaluation. Results of preformulation studies, FTIR, SEM, particle size and size distribution, % yield, drug content, buoyancy time, entrapment efficiency, in vitro dissolution and release kinetics. The FTIR Spectra revealed that, there was no interaction between polymers and Dasatinib. On the basis of release data of Dasatinib formulation F12 showed a good controlled release profile with maximum entrapment efficiency because of optimum polymer concentration i.e., 1:4 ratio (Eudragit S100) with sodium alginate than other drug: polymer ratios. The invitro dissolution data for best formulation F12 were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsemeyer-peppas equation. Optimized formulation F12 shows zero order drug release with Super case II transport mechanism.

Keywords: Dasatinib, Eudragit S100, sodium alginate, FTIR, SEM.

INTRODUCTION

Novel drug delivery system means of improving the therapeutic effectiveness of incorporated drugs by providing controlled delivery, targeting and sustained delivery. The drugs in to dosage for with the aim of sustaining drug levels and hence drug action is obtained for as prolong period of time in body. Microspheres are carrier drug delivery system which plays an important role in micro-particulate novel drug delivery system. Floating Microspheres are spherical, free flowing, monolithic matrix type. The main goal of the microspheres drug delivery system is to provide therapeutic amount of drug to the target site in the body. Microspheres are designed to release the drug in sustained and controlled manner, improving bioavailability, entrapment efficiency and lowering dose frequency of drug in the dosage form. [1-4]

Floating Microspheres are characterized by small spherical particles ranging from 10 millimeters to a thousand Floating millimeters [5]. Microspheres significantly improve patient compliance by enhancing the absorption of standard drugs while lowering side effects. The main benefit of employing microspheres as a medication delivery technology is the controlled release of the medicament. Floating Microsphere increases patient compliance by lowering dose frequency and maintaining a consistent medication plasma concentration [6].

MATERIALS & METHODS USED: Dasatinib API was procured from Dr. Reddy's Laboratories and HPMC Sodium alginate, Eudragit S-100, Ethyl Cellulose and NaHCO3 were procured from S D fine chemical Ltd, Mumbai, Xanthan gum, Calcium chloride, Hydrochloric acid was procured from Loba chemie Pvt. Ltd. Mumbai.

Solubility studies:

Dasatinib:

Solubility of Dasatinib was determined in water, 0.1 N HCl, pH 6.8 and pH 7.4 phosphate buffers. Solubility studies were performed by taking excess amount of Dasatinib in different beakers containing different solvents. The mixtures were shaken for 48hrs in rotary shaker. The solutions were centrifuged for 10mins at 1000 rpm and supernatant were analyzed at 323 nm by using UV Spectrophotometry.

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Determination of UV spectrum of Dasatinib:

10mg of Dasatinib was dissolved in 2ml of methanol then makeupto10ml with 0.1N HCl so as to get a stock solution of 1000 µg/ml concentration. From the above stock solution pipette out 1ml of the solution and makeup the volume to 10ml using 0.1N HCl to get the concentration of 100µg/ml concentration. From this stock solution pipette out 1ml of the solution and makeup the volume to 10ml using 0.1N HCl to get the concentration of 10µg/ml concentration, this solution was scanned under UV Spectroscopy using 200-400nm.

Preparation of standard calibration curve of Dasatinib in 0.1N HCl

Preparation of Standard Calibration Curve of Dasatinib in pH 1.2 Acidic buffer

10mg of Dasatinib was accurately weighed and transferred into 10ml volumetric flask. It was dissolved and diluted to volume with pH 1.2 Acidic buffer to give stock solution containing 1000µg/ml. The standard stock solution was then serially diluted with pH 1.2 Acidic buffer to get 5 to 30µg/ml of Dasatinib. The absorbance of the solution were measured against pH 1.2 Acidic buffer as blank at 323 nm using UV visible spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Drug-Excipient Compatibility Studies:

In the tablet dosage form the drug is in intimate contact with one or more excipients; the latter could affect the stability of the drug. Knowledge of drug- excipient interactions is therefore very useful to the formulator in selecting appropriate excipients. This information may be present for known drugs. For new drugs or new excipients, the preformulation studies must generate the needed information.

FT-IR Studies:

Physical compatibility studies were assured by FT-IR studies. The IR spectrums of the mixed powders were taken by preparing Potassium bromide pellets under dry condition by using pellet press. Spectra are superimposed. The transmission minimal (absorption maxima) in the spectra obtained with the sample corresponded in position and relative size to those in the spectrum obtained with the working/reference standards.

FORMULATION DESIGN

Table.1 Formulation design for Dasatinib Floating Microspheres using different ratios of drug & polymers.

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Dasatinib	100	100	100	100	100	100	100	100	100	100	100	100
Sodium Alginate	200	200	200	200	200	200	200	200	200	200	200	200
Ethyl Cellulose	100	200	300	400	-	-	-	-	-	-	-	-
Xanthan gum	-	-	-	-	100	200	300	400	-	-	-	-
Eudragit S-100	-	-	-	-	-	-	-	-	100	200	300	400
NaHCO3	25	25	25	25	25	25	25	25	25	25	25	25
Calcium	2	2	2	2	2	2	2	2	2	2	2	2

Preparation of Floating microspheres of Dasatinib:

Method used – ionic gelation method:

The floating microspheres containing Dasatinib were prepared by orifice ionic gelation technique. Sodium alginate along with in combination with different natural polymers and the gas forming agent sodium bicarbonate were dispersed in the purified water to form a homogeneous polymer mixture. The drug, Dasatinib was added to the polymer dispersion and mixed thoroughly on a magnetic stirrer to form a homogeneous dispersion. The gelation medium was prepared by dissolving calcium chloride in distilled water. The homogenous alginate solution was extruded using 21G syringe needle into the gelation medium. The distance between the edge of the needle and surface of gelation medium was about 10cms. The gel microspheres formed were left in the solution with gentle stirring for 30 min at room temperature to improve mechanic strength. After that, microsphere was collected and washed with distilled water twice, dried at room temperature for 24 hr and stored in desiccators.

Evaluation of Dasatinib Floating Microspheres:

Surface morphology (SEM)

Scanning electron microscopy has been used to determine particle size distribution, surface topography, texture, and to examine the morphology of fractured or sectioned surface. SEM is probably the most commonly used method for characterizing drug delivery systems, owing in large to simplicity of sample preparation and ease of operation. SEM studies were carried out by using JEOL JSM T-330A scanning microscope (Japan). Dry Dasatinib gel beads were placed on an electron microscope brass stub and coated with in an ion sputter. Picture of Dasatinib microspheres were taken by random scanning of the stub.

Particle size analysis:

The size of the prepared microspheres was measured by the optical microscopy method using a calibrated stage micrometer. Particle size was calculated by using equation.

$\lambda g = 10 X [(ni x \log xi) / N]$

Buoyancy behavior:

The time between the introduction of the FDDS into the medium and its buoyancy to the upper one third of the dissolution vessel (floating lag time) and the floating ability was determined using USP dissolution tester apparatus II (Paddle method). Fifty beads were put in the vessel and the paddles were rotated at 50 rpm in 900 ml 0.1 N HCl pH 1.2, maintained at 37±0.5 °C for 12 hours. The floating ability of the beads was measured by visual observation. The preparation was considered to have buoyancy, only when all beads floated on the test solution immediately or within a lag time which did not exceed 2 min.

Percentage yield

Percentage practical yield of Dasatinib microspheres was calculated to know about percentage yield or efficiency of any method, thus it helps in selection of appropriate method of production. Practical yield was calculated as the weight of Dasatinib beads recovered from each batch in relation to the sum of starting material.

The percentage yield of Dasatinib beads prepared was determined by using the formula.

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

Drug Entrapment Efficiency:

75mg of prepared floating alginate beads of Dasatinib were dissolved in 50 ml of 0.1N HCl (pH 1.2) and the drug content was analyzed at 323 nm using a UV/visible spectrophotometer (PG Instruments T60). Encapsulation efficiency was calculated as the percentage (w/w) of the theoretical drug content.

EE (%) = Actual Drug Content/ Theoretical Drug Content X 100

***In-vitro* dissolution studies:**

Procedure for *In-vitro* dissolution study

The release rate of Dasatinib floating Microspheres was determined by employing USP apparatus II (Paddle method). The dissolution test was performed using 900 ml 0.1N HCL, in 37 ±0.5°C at 50 rpm. Dasatinib floating microspheres equivalent to 100 mg of Dasatinib was used for the study. At various time points (hourly) 5ml of the sample solution was withdrawn from the dissolution apparatus for upto 12 hrs, and the samples were replaced with fresh dissolution medium. The samples were filtered and the absorbance was determined at 323 nm . Dissolution profiles of the formulations were analyzed by plotting cumulative percentage drug release versus time. The data obtained were also subjected to kinetic treatment to understand release mechanism.

Kinetics of drug release:[82-83]

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero order (Q v/s t), first order [Log(Q0-Q) v/s t], Higuchi's square root of time (Q v/s t1/2) and Korsemeyer Peppas double log plot (log Q v/s log t) respectively, where Q is the cumulative percentage of drug released at time t and (Q0-Q) is the cumulative percentage of drug remaining after time t. In short, the results obtained from in vitro release studies were plotted in four kinetics models of data treatment as follows.

- Cumulative percentage drug release Vs. Time (zero order rate kinetics)
- Log cumulative percentage drug retained Vs. Time (first order rate kinetics)
- Cumulative percentage drug release Vs. √T (Higuchi's classical diffusion equation)
- Log of cumulative percentage drug release Vs. log Time (Peppas exponential equation)

RESULTS AND DISCUSSION

Solubility Studies:

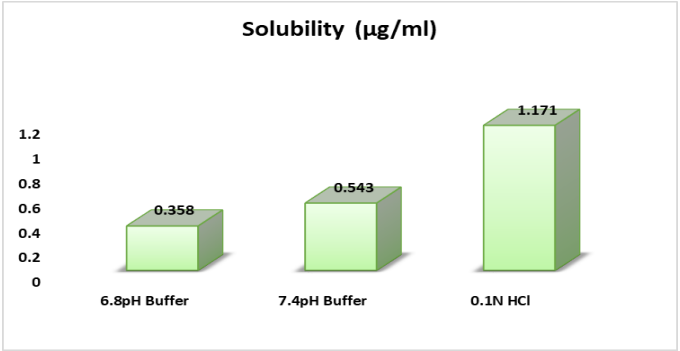

Figure.1 Solubility studies of Dasatinib

Discussion: From the solubility studies it was observed that the Dasatinib have higher solubility in 0.1N HCl than the other buffers.

UV spectrum of Dasatinib:

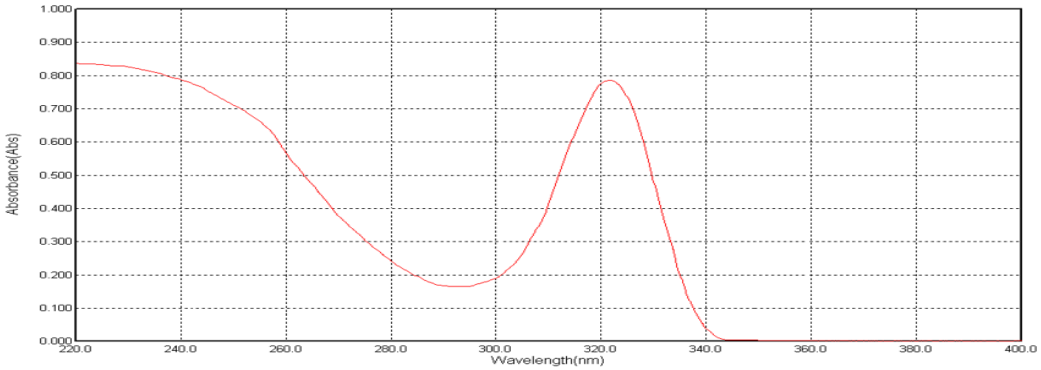

Figure.2 UV spectra of Dasatinib at 323 nm

Discussion: The λ-max of Dasatinib of 100% solution i.e 12ppm (µg/ml) by using Single Beam Spectrophotometer (YIS-294) was found to be at 323 nm by using 0.1N HCl.

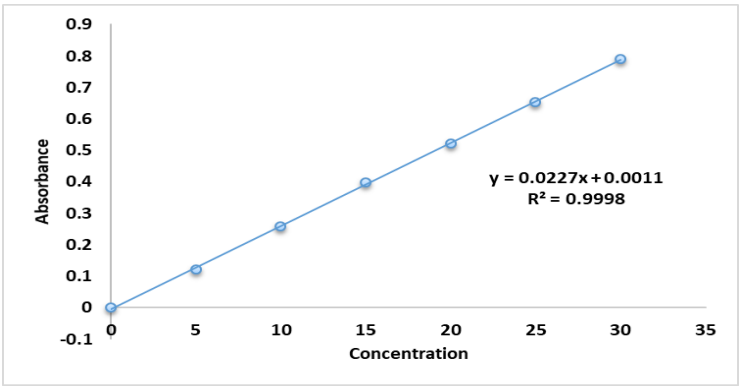

Figure.3 Standard calibration curve of Dasatinib in 0.1N HCl at 323 nm

Discussion: The linearity was found to be in the range of 5-30µg/ml in acetone, pH 1.2 HCl buffer. The regression value was found to be 0.998 which less closer to 1 indicating the method obeyed Beer-lamberts' law.

FT-IR SPECTROSCOPY STUDY.

In the present study FT-IR data of drug and excipient was compared with standard spectrum of pure drug. The characteristic peaks associated with specific functional groups and bonds of the molecule and their presence/absence in the polymer carrier formulation were noted. The IR spectra showed that there is no significant evidence for interaction between the drug and the excipients.

Pure Drug

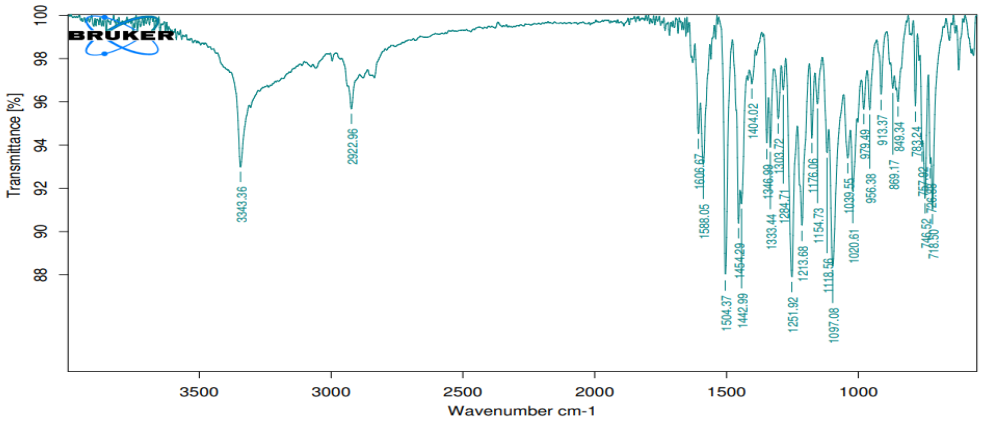

Figure.4 IR spectra of Dasatinib pure

Optimized Formulation:

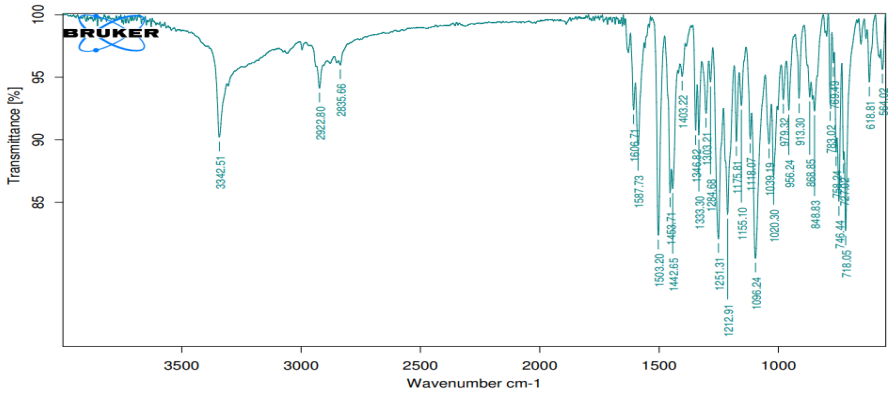

Figure.5 IR spectra of Dasatinib + Excipients

Discussion: The IR spectrum of pure drug was found to be similar to the standard spectrum of Dasatinib. From the spectra of Dasatinib, combination of Dasatinib with polymers, it was observed that all characteristic peaks of Dasatinib were not altered and present without alteration in the combination spectrum, thus indicating compatibility of the drug and excipients.

Evaluation of Dasatinib Floating Microspheres

Surface morphology - Scanning Electron Microscopy (SEM)

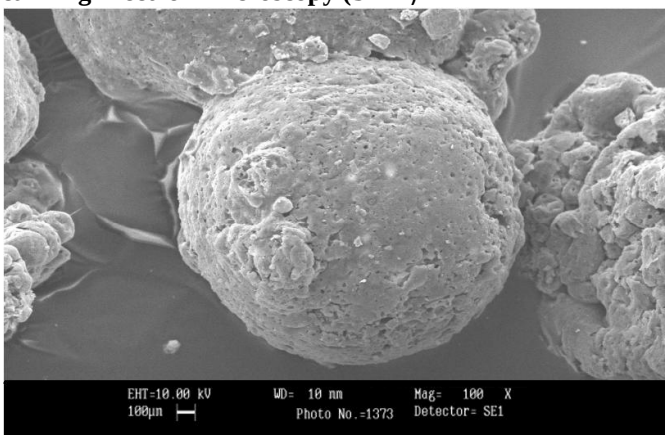

Figure.6 SEM photographs of floating microspheres using sodium alginate and Eudragit S-100

Discussion:

From the results of SEM analysis it was observed that the surface area of Microspheres was spherical and found to be rigid in nature, due to the higher polymer concentration, and the viscosity of the sodium alginate and Eudragit S-100. The surface morphology of the Dasatinib floating microspheres was studied by SEM. SEM photographs of the optimized formulation. Surface morphology of the Dasatinib microspheres was found to be spherical with rigid nature.

Determination of Average particle size

Table.2 Average diameter of Dasatinib floating microspheres.

Formulation code	Average size (µm)
F1	150
F2	120
F3	110
F4	126
F5	135
F6	120
F7	145
F8	160
F9	100
F10	105
F11	110
F12	100

Discussion: As the ratio of polymer was increased, the mean particle size of Dasatinib spheres had also decreased. The significant decrease may be due to the increase in the viscosity of the droplets. Dasatinib floating microspheres having a size range of 100 to 160 micro meter with normal frequency distribution was obtained.

Percentage yield & Entrapment Efficiency

Table.3 Drug entrapment efficiency of Dasatinib Floating Microspheres

Sl. No.	Formulation Code	Percentage Yield(%)	Entrapment Efficiency (%)
1	F1	93.02±1.47	50.67±1.74
2	F2	94.43±1.25	54.24±1.20
3	F3	95.40±1.09	59.16±1.45
4	F4	96.35±1.56	64.39±1.34
5	F5	94.71±1.20	58.42±1.67
6	F6	96.23±1.74	64.05±1.41
7	F7	97.01±1.36	68.38±1.92
8	F8	98.74±1.14	70.42±1.02
9	F9	95.53±1.45	65.16±1.45
10	F10	96.78±1.75	68.27±1.74
11	F11	98.81±1.54	71.54±1.20
12	F12	99.24±1.62	74.13±1.68

Discussion: Entrapment efficiency increased with increase in the polymer concentration. From the results it can be inferred that there is a proper distribution of Dasatinib in the microspheres and the deviation were within the acceptable limits. By increasing the polymer concentration, the encapsulation efficiency was increased.

In vitro dissolution studies

Table.4 In vitro evaluation of Dasatinib Floating microspheres from F1-F12

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	32.42 ±1.48	20.37 ±1.45	27.08 ±1.57	24.14 ±1.37	21.43 ±1.17	24.66 ±1.37	17.45 ±1.58	15.20 ±1.78	37.58 ±1.20	19.84 ±1.37	22.78 ±1.54	24.45 ±1.21
2	41.33 ±1.16	36.54 ±1.85	34.89 ±1.61	35.26 ±1.45	30.75 ±1.20	34.19 ±1.45	22.16 ±1.46	24.36 ±1.15	45.61 ±1.45	25.26 ±1.45	29.48 ±1.74	31.75 ±1.45
3	54.15 ±1.45	45.60 ±1.30	40.58 ±1.85	42.61 ±1.68	42.16 ±1.45	45.52 ±1.89	29.63 ±1.79	36.12 ±1.36	52.48 ±1.14	32.56 ±1.12	38.41 ±1.83	38.12 ±1.74
4	62.75 ±1.84	52.63 ±1.42	47.63 ±1.45	49.85 ±1.42	52.36 ±1.67	52.16 ±1.52	35.64 ±1.51	42.86 ±1.45	62.84 ±1.62	45.28 ±1.52	48.21 ±1.51	45.30 ±1.62
5	71.65 ±1.37	64.89 ±1.36	51.25 ±1.39	55.34 ±1.47	62.24 ±1.47	61.52 ±1.02	42.79 ±1.45	50.25 ±1.74	68.74 ±1.45	53.65 ±1.75	59.62 ±1.46	52.15 ±1.51
6	77.36 ±1.78	72.22 ±1.45	59.32 ±1.45	60.27 ±1.69	73.16 ±1.85	69.37 ±1.45	52.15 ±1.20	55.67 ±1.85	74.52 ±1.75	65.84 ±1.10	64.26 ±1.25	60.56 ±1.48
7	85.81 ±1.51	80.34 ±1.12	66.42 ±1.52	67.12 ±1.45	81.63 ±1.20	76.85 ±1.67	60.25 ±1.47	62.94 ±1.12	85.71 ±1.52	72.84 ±1.99	78.21 ±1.84	68.72 ±1.32
8	96.74 ±1.69	88.37 ±1.47	72.18 ±1.42	74.53 ±1.85	89.75 ±1.45	87.67 ±1.43	72.63 ±1.56	73.42 ±1.52	91.64 ±1.46	86.91 ±1.36	85.26 ±1.51	75.22 ±1.41
9		98.06 ±1.58	80.66 ±1.19	83.49 ±1.95	95.68 ±1.16	98.28 ±1.12	84.98 ±1.85	83.43 ±1.34	98.56 ±1.85	92.68 ±1.54	91.42 ±1.75	82.32 ±1.48
10			89.67 ±1.45	90.78 ±1.36			90.65 ±1.36	90.34 ±1.69		98.19 ±1.75	95.26 ±1.69	88.65 ±1.45
11			96.42 ±1.75	97.48 ±1.42				96.25 ±1.45			98.36 ±1.45	93.41 ±1.75
12												99.22 ±1.59

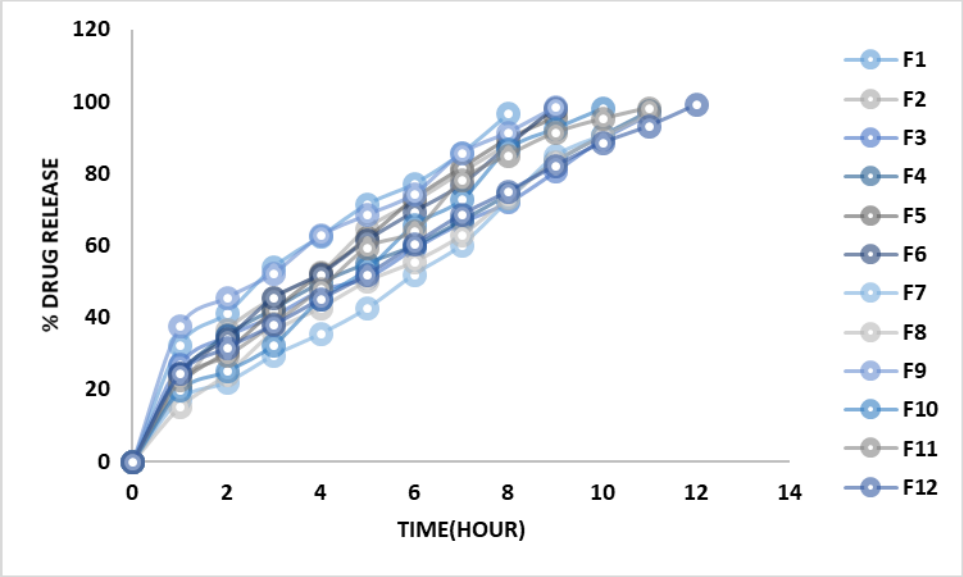

Figure.7 % Cumulative drug release of F1-F12

Discussion:

The in vitro performance of Dasatinib floating microspheres showed prolonged and controlled release of Dasatinib. The results of the in vitro dissolution studies showed controlled release in a predictable manner. As the polymer concentration was increased, the drug release from the floating microspheres were found to decrease. Here polymer concentration increased with polymer 1:4 ratio like Eudragit S-100. Compare to all formulation, F12 formulation shows prolong drug release at the end of 12 hours. The in vitro release profiles of all the formulations (F1 to F12) are shown in tables and Fig.

Drug Release Kinetics:

Zero Order:

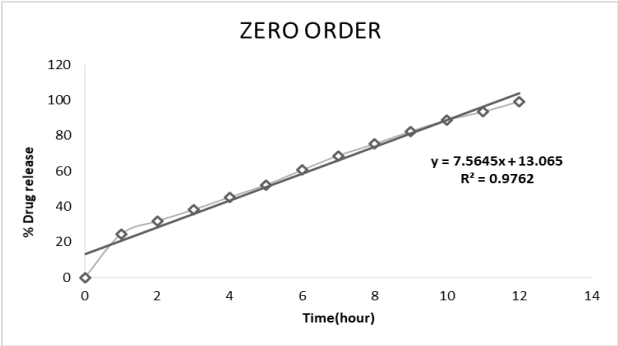

Figure.8 Zero order graph of F12 formulation

First Order:

Figure.9 First order graph of F12 formulation

Higuchi plot:

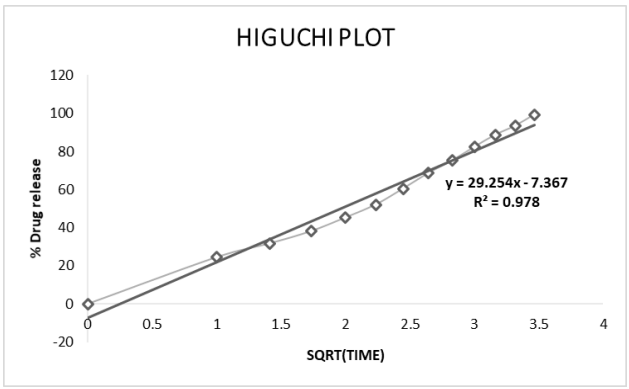

Figure.10 Higuchi plot of F12 formulation

Peppas plot:

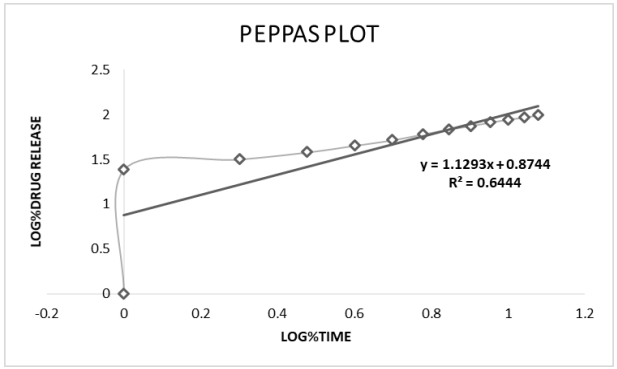

Figure.11 Peppas plot of F12 formulation

Discussion: From the drug release kinetics of the Dasatinib floating Microspheres, it was concluded that the formulation F12 follows zero order drug release with super case-II transport mechanism.

SUMMARY AND CONCLUSION

The concept of formulating floating microspheres containing Dasatinib offers a suitable, practical approach to achieve a prolonged therapeutic effect by continuously releasing the medication over extended period of time. In present work, floating microspheres of Dasatinib were prepared successfully by ionotropic gelation method using different polymers.

From the above experimental results it can be concluded that:

- Preformulation studies like melting point, solubility and UV analysis complied with standards.
- The FTIR Spectra revealed that, there was no interaction between Dasatinib and polymers .
- Surface smoothness of the Dasatinib floating microspheres was confirmed by SEM.
- As the ratio of polymer was increased, the mean particle size of Dasatinib floating microspheres was decreased. Dasatinib floating microspheres with normal frequency distribution were obtained.
- From the results of entrapment efficiency it can be inferred that there was a proper distribution of Dasatinib in the microspheres and the deviation was within the acceptable limits.
- The study also indicated that the amount of drug release decreases with an increase in the polymer concentration. The in vitro performance of Dasatinib Floating microspheres showed prolonged and controlled release of drug, with Xanthan gum and Ethyl Cellulose and Eudragit s100.
- From the drug release kinetics of the Dasatinib floating Microspheres, it was concluded that the formulation F12 follows zero order drug release with super case-II transport mechanism.
- Based upon the preliminary data and in vitro dissolution studies of Dasatinib floating microspheres it was concluded that the formulation of floating microspheres was successfully formulated by using sodium alginate along with Eudragit S100 in 1:4 ratio.

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