CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.7829719

Available online at: http://www.iajps.com *Research Article*

FORMULATION AND *IN VITRO* CHARACTERIZATION OF IBRUTINIB EXTENDED RELEASE TABLETS

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Article Received: January 2023 **Accepted:** February 2023 **Published:** March 2023

Abstract:

The aim of the present study was to develop extended release formulation of Ibrutinib to maintain constant therapeutic levels of the drug for over 12 hrs. HPMC K100M, HPMC (K4M) and Carbopol 71 G were employed as polymers. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F6) showed better and desired drug release pattern i.e., 98.85% in 12 hours. It contains the HPMC (K4M) as Extended release material. It followed peppas release kinetics mechanism.

Keywords: *Ibrutinib, Extended release system.*

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Please cite this article in press M. Gnana Sowmya et al, ***Formulation And In Vitro Characterization Of Ibrutinib Extended Release Tablets.,*** *Indo Am. J. P. Sci, 2023; 10 (04).*

INTRODUCTION:

The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes. The terms Sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. [1,2]

There are several reasons for attractiveness of these dosage forms: provides increased bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak trough concentration and side effects and possibly improves the specific distribution of the drug. If one were to develop an ideal drugdelivery system, two pre-requisites would be required: Firstly single dose for the duration of treatment whether for days or weeks as with infection, diabetes orhypertension. Second it should deliver the active entity directly to the site of action minimizing the side effects.

There are certain considerations for the preparation of extended release formulations: If the active compound has a long half-life, it is sustained on its own, If the pharmacological activity of the active is not directly related to its blood levels, If the absorption of the drug involves an active transport and If the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose. The above factors need serious review prior to design.[3]

Extended release formulations make the drug available over extended time period after oral administration. The extended release product will optimize therapeutic effect and safety of a drug at the same time improving the patient convenience and compliance. By incorporating the dose for 24 hrs into one tablet/capsule from which the drug is released slowly. This formulation helps to avoid the side effects associated with low and high concentrations. The ideal drug delivery system should show a constant zero-order release rate and maintain the constant plasma concentrations.

It is desirable to maintain a therapeutic blood concentration in order to achieve the desirable pharmacological effects. To maintain a narrow range of therapeutic blood concentration it is desirable to have a dosage form that can deliver the drug in a more sustainable or controlled way to achieve the desired results. Extended release tablets and capsules are commonly taken once or twice daily, compared with counterpart conventional forms that may have to be taken three or four times daily to achieve the same therapeutic effect. Typically, extended release products provide an immediate release of drugs that promptly produces the desired therapeutic effect, followed by gradual release of additional amount of drugs to maintain this effect over a predetermined period. The sustained plasma drug levels provided by extended release products often eliminate the need for night dosing, which benefits not only the patient but the patient but the caregiver as well.[4]

Drawbacks of Conventional Dosage Form [5]:

- Poor patient compliance, increased chances of missing the dose of a drug with short halflife for which frequent administration is necessary.
- The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
- A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
- The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.

Advantages of Extended Release Delivery System [6]:

- The extended release formulations reduce dosing frequency of drugs.
- The extended release formulations may maintain therapeutic concentrations.
- Reduce the toxicity by slowing drug absorption.
- The use of these formulations avoids the high blood concentration.
- Extended release formulations have the potential to improve the patient compliance and convenience.
- Minimize the local and systemic side effects.
- Increase the stability by protecting the drug from hydrolysis or other degradative changes in gastrointestinal tract.
- Improvement in treatment efficacy.
- Minimize drug accumulation with chronic dosing.
- Improve the bioavailability of some drugs.
- Usage of less total drug.

- Improve the ability to provide special effects. For example, Morning relief of arthritis through bed time dosing.

Disadvantages of Extended Release Delivery System [6]:

- Extended release formulation contains a higher drug load and thus any loss of integrity of the release characteristics of the dosage form.
- The larger size of extended release products may cause difficulties in ingestion or transit through gut.
- The release rates are affected by various factors such as food and the rate of transit through the gut.
- Some differences in the release rate from one dose to another dose but these have been minimized by modern formulations.
- High cost of preparation.
- Sometimes the target tissue will be exposed to constant amount of drug over extended period results in drug tolerance.

Rationale of Extended Drug Delivery [7]:

The main objective to formulate an API in an extended drug delivery system is related to its pharmacokinetics parameters. An appropriate formulation can make the absorption, distribution, metabolism and elimination (ADME) profile of a drug much more favourable. This change of the ADME can have a profound impact on many aspects of the clinical use of the drug from patient compliance and convenience to its very efficacy, tolerance and safety parameters.

Pellets:

Pelletization is an agglomeration process, that converts fine powder blend of drug(s) and excipients into small, free flowing, spherical units, referred to as pellets. Rationale of extended release pellets Pellets provide the development scientist with a high degree of flexibility during the design and development of oral dosage forms. They can be divided into desired dose strengths without formulation or process changes, and can also be blended to deliver incompatible bioactive agents simultaneously or particles with different release profiles at the same site or at different sites within the gastrointestinal tract.

Advantages of extended release pellets:

- Reduce dosing frequency of drugs.
- Maintain therapeutic concentrations.
- Reduce the toxicity by slowing drug absorption.
- The use of pellets avoids the high blood concentration.
- Extended release formulations have the potential to improve the patient compliance and convenience.
- Minimize the local and systemic side effects.
- Increase the stability by protecting the drug from hydrolysis or other degradative changes in gastrointestinal tract.
- Improvement in treatment efficacy.
- Minimize drug accumulation with chronic dosing.
- Improve the bioavailability of some drugs.
- Usage of less total drug.
- Improve the ability to provide special effects. [8]

- **Drugs those are Unsuitable for Such Design:**
- Elimination half-life less than 2 hours. ·
- Administered in large dose. ·
- Therapeutics index is narrow. ·
- Poor water solubility. ·
- Long elimination half-life.
- Drugs having extensive first-pass clearance. [9,10,11,12]

Approaches to Achieve Extended Release Matrix Tablet:

The purpose of designing ER dosage form is to develop a reliable formulation that has all the advantages of immediate release dosage form and yet devoid of the dose dumping. The fundamental principle in design of extended release tablet are to slowing down of absorption, bio transformation and excretion rate respectively. Various techniques have been used in the formulation of ER products. In general, extended formulations can be divided into different categories based on the mechanism of drug release.

1) Diffusion controlled release system.
2) Dissolution controlled release system.
3) Ion exchange resin drug complex.
4) Swelling controlled release

MATERIALS:

Ibrutinib Procured From Hetero Laboratories Ltd, Provided by SURA LABS, Dilsukhnagar, Hyderabad., HPMC K100M Merck Specialities Pvt Ltd, Mumbai, India, HPMC (K4M) Merck Specialities Pvt Ltd, Mumbai, India, Carbopol 71 G Merck Specialities Pvt Ltd, Mumbai, India, PVP K 30 Merck Specialities Pvt

Ltd, Mumbai, India, MCC102 Merck Specialities Pvt Ltd, Mumbai, India, Mg. stearate Merck Specialities Pvt Ltd, Mumbai, India, Talc Merck Specialities Pvt Ltd, Mumbai, India

METHODOLOGY:

Analytical method development:

Determination of absorption maxima:

100mg of Ibrutinib pure drug was dissolved in 15ml of Methanol and make up to 100ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with 100 ml by using 0.1 N HCL (stock solution-2 i.e. 100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCL (10µg/ml). Scan the 10 10µg/ml using Double beam UV/VIS spectrophotometer in the range of 200 – 400 nm.

Preparation calibration curve:

100mg of Ibrutinib pure drug was dissolved in 15ml of Methanol and volume make up to 100ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with100ml by using 0.1 N HCl (stock solution-2 i.e. 100µg/ml). From this take 1, 2, 3, 4 and 5 ml of solution and make up to 10ml with 0.1N Hcl to obtain 10, 20, 30, 40 and 50 µg/ml of Ibrutinib per ml of solution. The absorbance of the above dilutions was measured at 258 nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

Formulation development of Extended release Tablets:

All the formulations were prepared by direct compression method. The compositions of different formulations are given in Table 7.1. The tablets were prepared as per the procedure given below and aim is to prolong the release of Ibrutinib.

Procedure:

1) Ibrutinib 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.

Table1: Formulation of Extended release tablets

INGREDIENTS	FORMULATION CODE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ibrutinib	140	140	140	140	140	140	140	140	140
HPMC K100M	20	40	60	-	-	-	-	-	-
HPMC (K4M)	-	-	-	20	40	60	-	-	-
Carbopol 71 G	-	-	-	-	-	-	20	40	60
PVP K 30	10	10	10	10	10	10	10	10	10
MCC102	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Mg. Stearate	5	5	5	5	5	5	5	5	5
Talc	3	3	3	3	3	3	3	3	3
Total weight (mg)	300	300	300	300	300	300	300	300	300

All the quantities were in mg

RESULTS AND DISCUSSION:

The present work was designed to developing extended tablets of Ibrutinib using various polymers. All the

formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Standard graph of Ibrutinib in 0.1N HCl:

The scanning of the 10µg/ml solution of Ibrutinib in the ultraviolet range (200-400 nm) against 0.1 N HCl blank gave the λ_{max} as 258 nm. The standard concentrations of Ibrutinib (10-50 µg/mL) prepared in 0.1N HCl showed good linearity with R^2 value of 0.999, which suggests that it obeys the Beer-Lamberts law.

Table 2: Standard curve of Ibrutinib in 0.1N HCl

Concentration (µg/ mL)	Absorbance
0	0
10	0.119
20	0.234
30	0.345
40	0.461
50	0.572

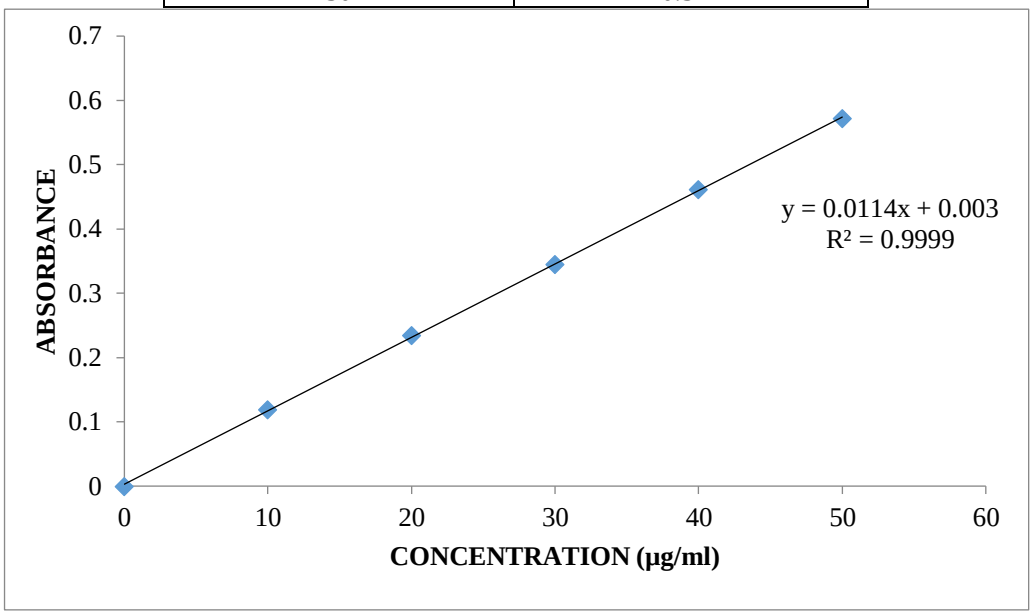

Fig1. : Calibration curve of Ibrutinib in 0.1N HCl at 258 nm

Table3 Standard curve of Ibrutinib in Phosphate buffer pH 6.8

Concentration (µg / ml)	Absorbance
0	0
10	0.131
20	0.254
30	0.385
40	0.512
50	0.629

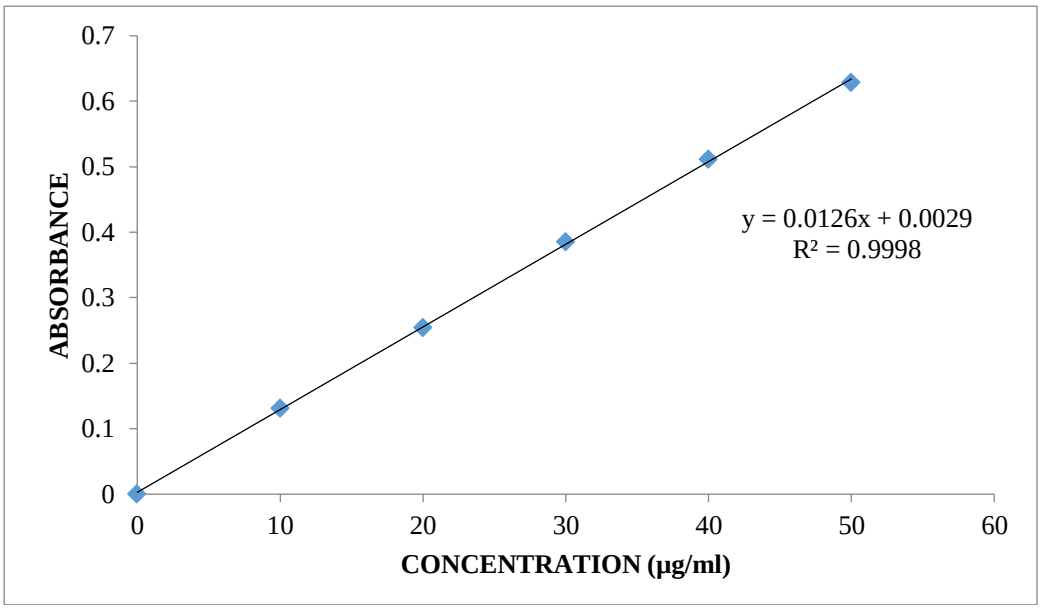

Fig.2: Calibration of Ibrutinib in Phosphate buffer pH 6.8

Preformulation parameters of powder blend

Table 4:Pre-compression parameters of powder blend

Formulation Code	Angle of Repose	Bulk density (gm/cm^3)	Tapped density (gm/ cm^3)	Carr's index (%)	Hausner's Ratio
F1	25.01	0. 59	0.57	14.03	1.16
F2	26.8	0. 46	0.67	16.41	1.19
F3	27.7	0. 32	0. 54	18.75	1.23
F4	25.33	0.54	0.64	15.62	1.18
F5	25.24	0.52	0.65	18.46	1.22
F6	28.12	0. 46	0. 56	15.15	1.17
F7	27.08	0.58	0.69	15.94	1.18
F8	25.12	0.48	0.67	15.78	1.18
F9	26.45	0.54	0.65	16.92	1.25

All the values represent n=3

Quality control parameters for tablets:

Table5: Post Compression Parameters of Tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	298.62	5.9	0.52	3.16	96.35
F2	296.35	5.1	0.34	3.56	99.61
F3	299.21	5.6	0.62	3.41	98.52
F4	297.49	5.2	0.41	3.22	97.42
F5	295.32	5.8	0.26	3.61	97.12
F6	299.58	5.1	0.39	3.25	99.33
F7	297.96	5.7	0.65	3.42	98.64
F8	299.67	5.9	0.73	3.13	95.78
F9	298.32	5.5	0.15	3.24	96.41

***In Vitro* Drug Release Studies**

Table6: Dissolution Data of Ibrutinib Tablets Prepared with HPMC K100M in Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED		
	F1	F2	F3
0	0	0	0
0.5	25.32	20.04	18.63
1	34.53	27.56	21.63
2	49.90	34.35	28.52
3	54.96	43.52	31.31
4	59.14	48.75	38.25
5	62.85	52.54	45.78
6	73.92	59.26	50.17
7	80.41	65.95	57.79
8	89.61	70.14	62.27
9	93.17	73.45	69.64
10	96.33	81.57	74.87
11		98.18	84.10
12			98.64

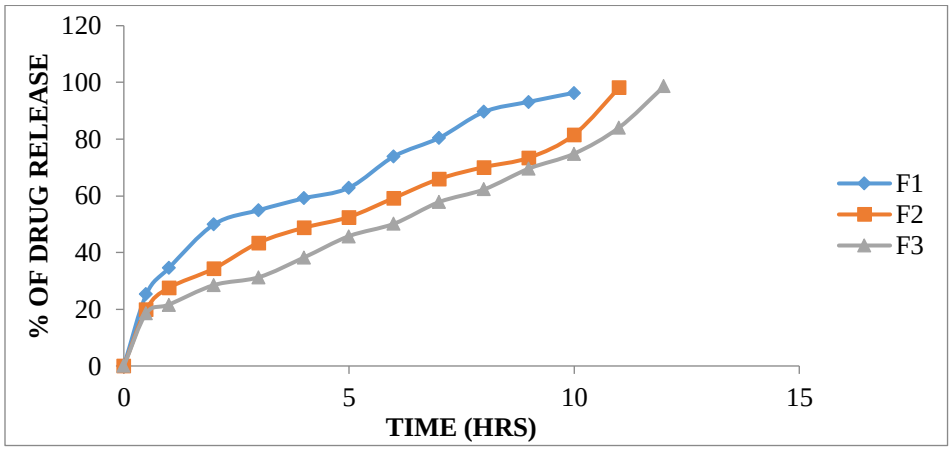

Figure 3: Dissolution study of Ibrutinib extended tablets (F1 to F3)

Table 7: Dissolution Data of Ibrutinib tablets Prepared with HPMC (K4M) in Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED		
	F4	F5	F6
0	0	0	0
0.5	15.17	13.90	10.49
1	22.12	19.45	16.63
2	36.64	25.02	27.55
3	42.20	31.31	33.21
4	48.56	37.82	40.96
5	55.43	43.47	45.11
6	58.01	50.74	55.28
7	67.57	54.05	61.71
8	73.91	57.93	67.34
9	79.41	63.26	74.98
10	83.72	75.45	80.74
11	86.02	80.36	86.12
12	90.14	95.47	98.85

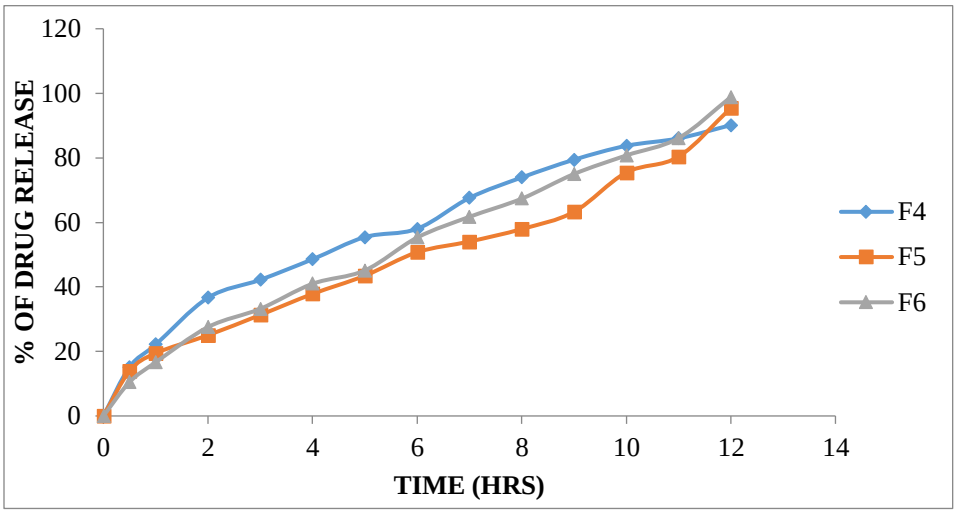

Figure 4: Dissolution study of Ibrutinib tablets (F4 to F6)

Table 8: Dissolution Data of Ibrutinib tablets Prepared with Carbopol 71 G in Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED		
	F7	F8	F9
0	0	0	0
0.5	20.56	17.58	10.62
1	26.45	23.20	15.28
2	31.23	27.35	20.95
3	40.54	34.14	25.51
4	49.73	39.75	29.32
5	56.46	43.09	33.96
6	58.12	46.16	39.78
7	62.59	55.75	44.35
8	71.41	60.11	50.62
9	78.98	64.67	56.43
10	83.24	68.34	60.02
11	89.72	76.40	64.10
12	90.14	85.18	70.16

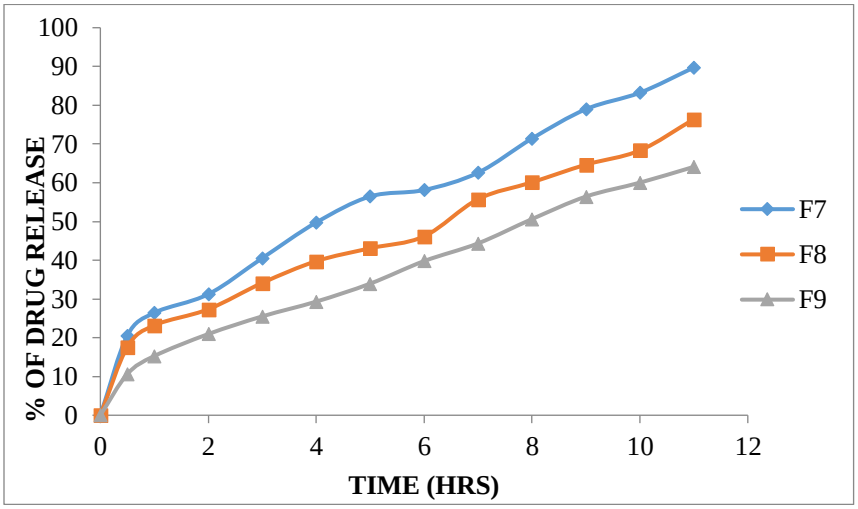

Figure 5: Dissolution study of Ibrutinib tablets (F7 to F9)

Table 9: Release kinetics data for optimized formulation (F6)

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
10.49	**0.5**	0.707	1.021	-0.301	1.952	20.980	0.0953	-0.979	89.51	4.642	4.473	0.168
16.63	**1**	1.000	1.221	0.000	1.921	16.630	0.0601	-0.779	83.37	4.642	4.369	0.273
27.55	**2**	1.414	1.440	0.301	1.860	13.775	0.0363	-0.560	72.45	4.642	4.169	0.473
33.21	**3**	1.732	1.521	0.477	1.825	11.070	0.0301	-0.479	66.79	4.642	4.057	0.584
40.96	**4**	2.000	1.612	0.602	1.771	10.240	0.0244	-0.388	59.04	4.642	3.894	0.748
45.11	**5**	2.236	1.654	0.699	1.739	9.022	0.0222	-0.346	54.89	4.642	3.800	0.841
55.28	**6**	2.449	1.743	0.778	1.651	9.213	0.0181	-0.257	44.72	4.642	3.550	1.092
61.71	**7**	2.646	1.790	0.845	1.583	8.816	0.0162	-0.210	38.29	4.642	3.371	1.271
67.34	**8**	2.828	1.828	0.903	1.514	8.418	0.0149	-0.172	32.66	4.642	3.196	1.445
74.98	**9**	3.000	1.875	0.954	1.398	8.331	0.0133	-0.125	25.02	4.642	2.925	1.717
80.74	**10**	3.162	1.907	1.000	1.285	8.074	0.0124	-0.093	19.26	4.642	2.681	1.961
86.12	**11**	3.317	1.935	1.041	1.142	7.829	0.0116	-0.065	13.88	4.642	2.403	2.238
98.85	**12**	3.464	1.995	1.079	0.061	8.238	0.0101	-0.005	1.15	4.642	1.048	3.594

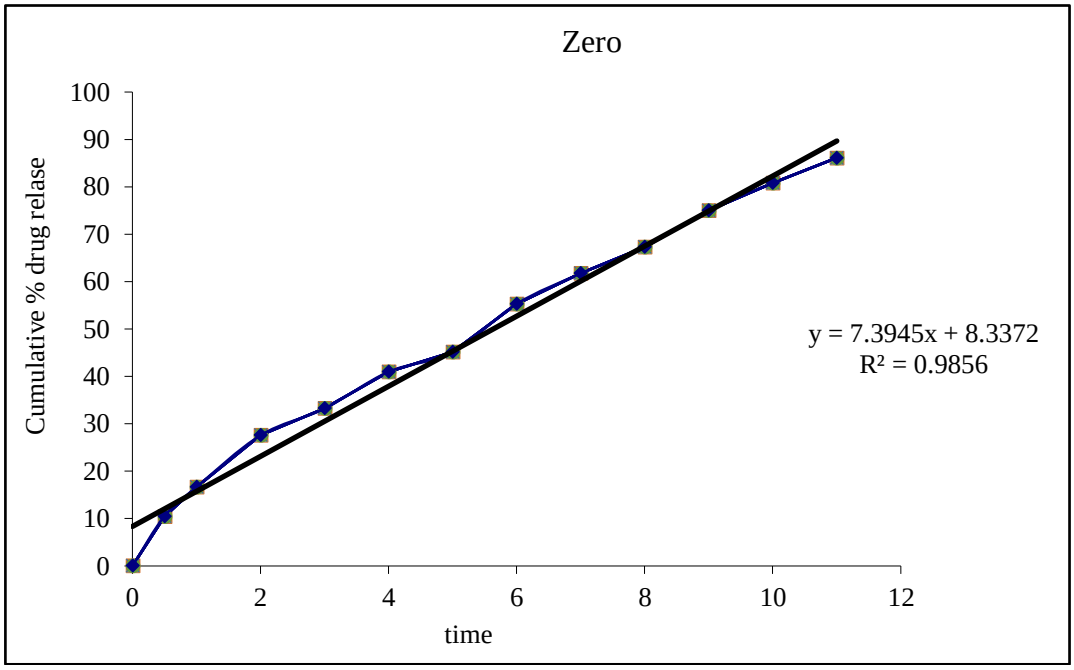

Figure 6: Graph of zero order kinetics

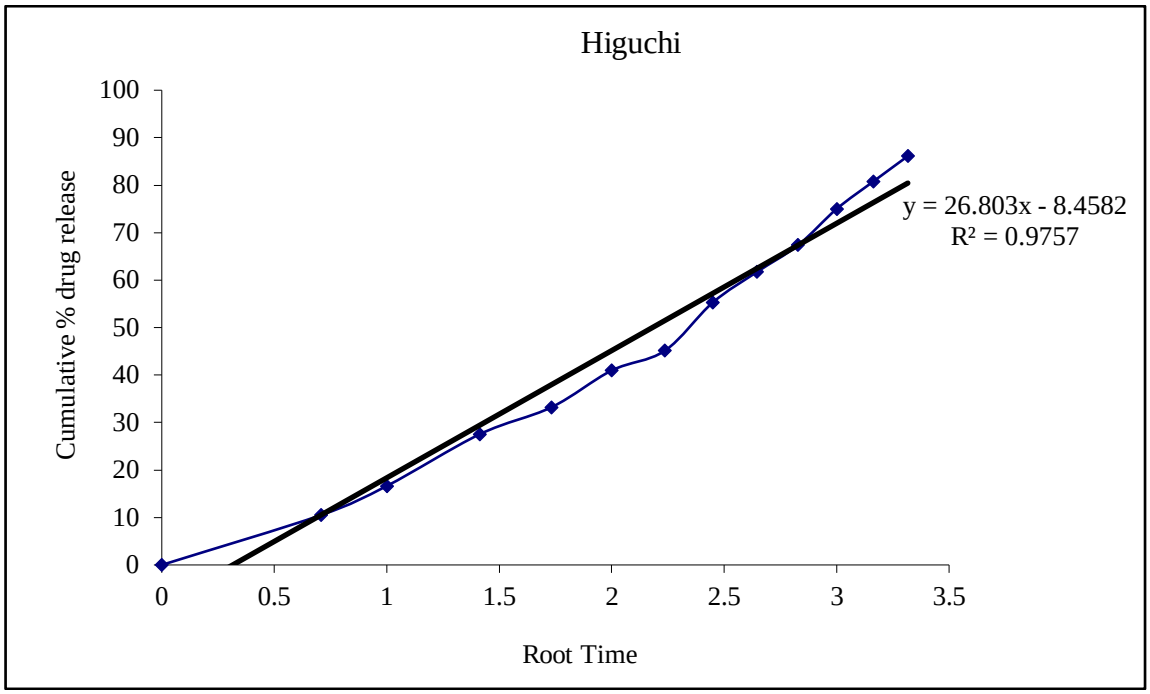

Figure 7: Graph of higuchi release kinetics

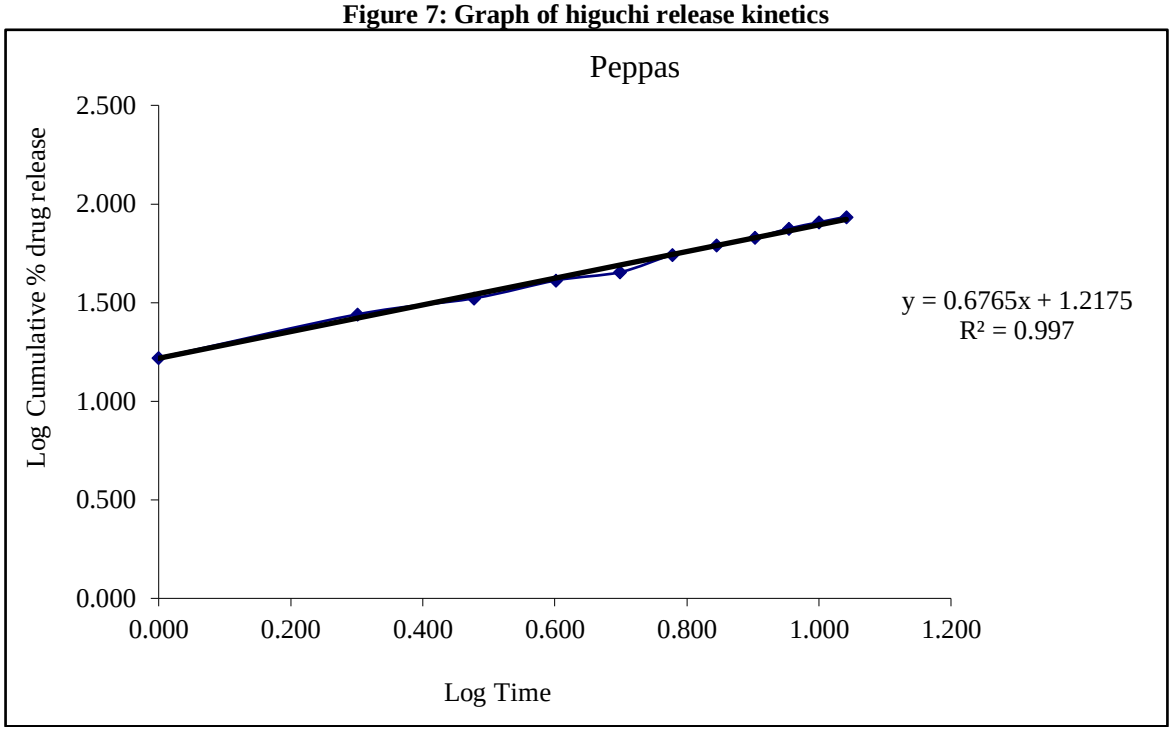

Figure 8: Graph of peppas release kinetics

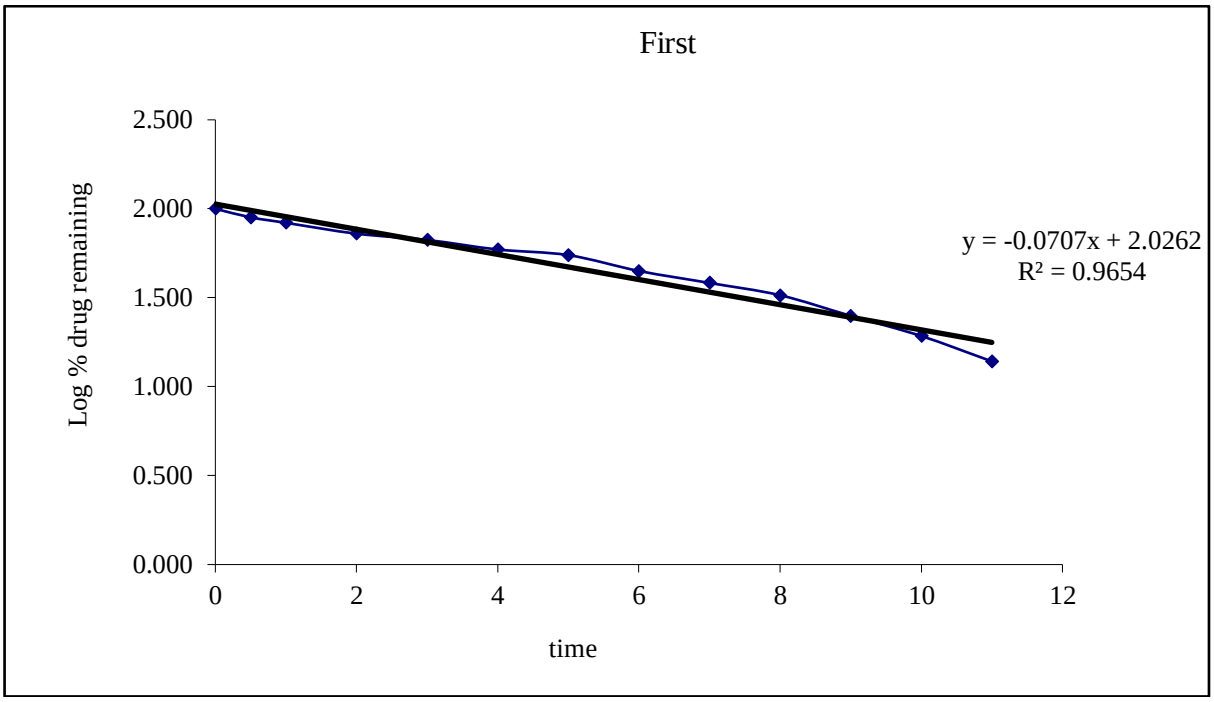

Figure 9: Graph of first order release kinetics

Drug – Excipient compatibility studies

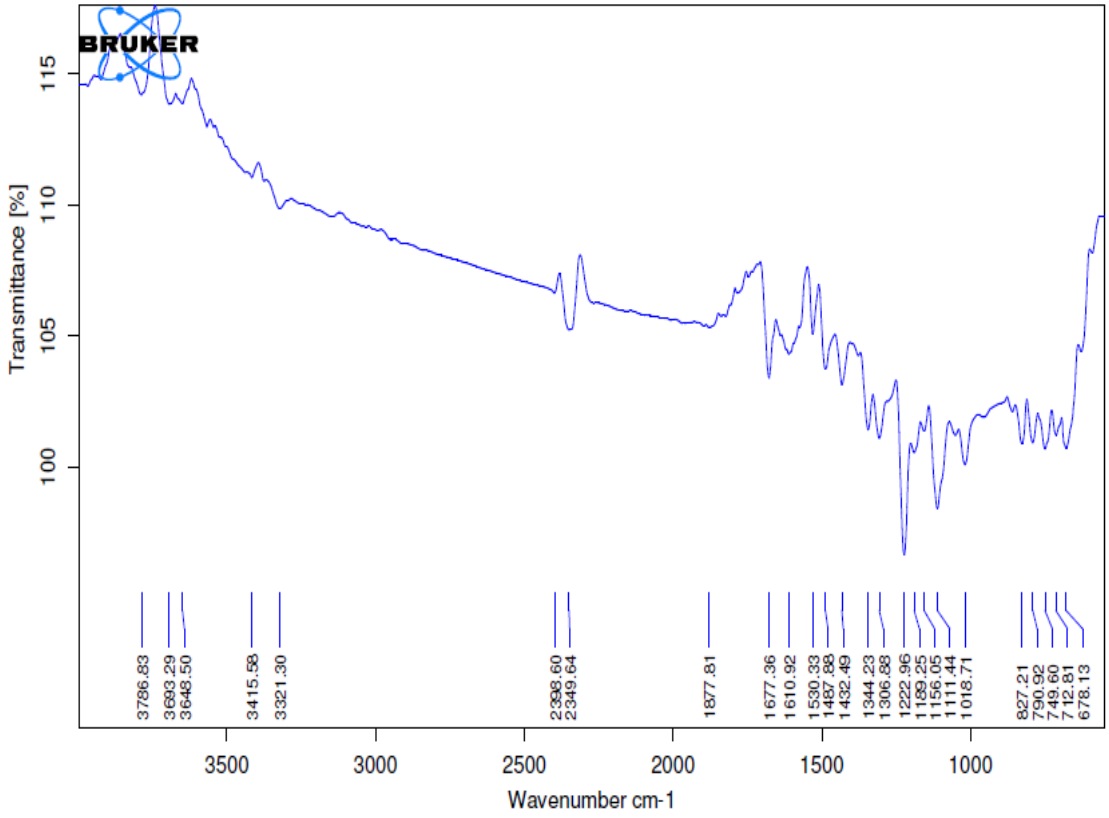

Fig 10: FTIR Graph of Pure Drug of Ibrutinib

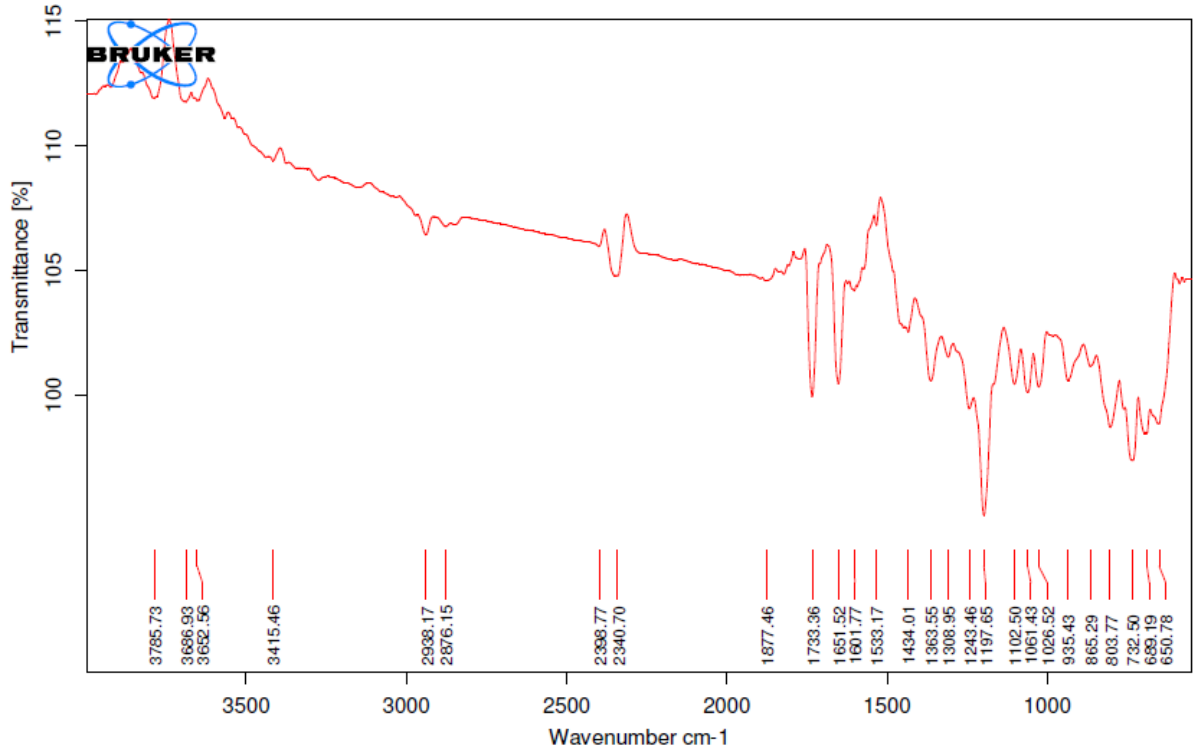

Fig11: FTIR Graph of Pure Drug of Ibrutinib Optimized Graph

CONCLUSION:

The present study concludes that extended drug delivery of Ibrutinib tablets can be a good way to prolong duration of action of drug by reducing the frequency of dosing of Ibrutinib. Present study concludes that extended drug delivery system should be a suitable method for Ibrutinib administration. The optimized formulation was found to be F6 formulation.

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