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Formulation and invitro evaluation of extended release tablet of ibrutinib

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ABSTRACT

The aim of the present study was to develop Ibrutinib extended release tablets to maintain constant therapeutic levels of the drug for over 12 hrs. Guar gum, Karaya gum and Acacia were used as polymers. All the formulations were passed various physicochemical evaluation parameters such as Bulk Density, Tapped Density, Carr's Index, Hausners Ratio, Angle of Repose, Weight Variation, Hardness, Thickness, Friability and Drug Content. From the dissolution studies it was evident that the formulation I6 showed better and desired drug release pattern i.e., 99.14 % in 12 hours. It contains the Karaya gum as polymer. It followed Kars mayer peppas release kinetics mechanism. In conclusion the results suggest that the developed matrix tablets of Ibrutinib could perform therapeutically better than conventional dosage form, leading to improved efficacy and better patient compliance.

Keywords: Ibrutinib, Guar gum, Karaya gum, Acacia and Extended release tablets.

INTRODUCTION

Historically, oral drug administration has been the predominant route for drug delivery. It is known to be the most popular route of drug administration due to the fact the gastrointestinal physiology offers more flexibility in dosage form design than most other routes. A major challenge for the pharmaceutical industry in drug development is to produce safe and efficient drugs, therefore properties of drugs and the way in which they are delivered must be optimized.

A controlled release drug delivery system delivers the drug locally or systemically at a predetermined rate for a specified period of time. The goal of such systems is to provide desirable delivery profiles that can achieve therapeutic plasma levels. Drug release is dependent on polymer properties, thus the application of these properties can produce well characterised and reproducible dosage forms.

Oral route still remains the most popular for drug administration by virtue of its convenience to the patient. A sizable portion of orally administered dosage forms, so called conventional, are designed to achieve maximal drug bioavailability by maximizing the rate and extent of absorption. While such dosage forms have been useful, frequent daily administration is necessary, particularly when the drug has a short biological half life. This may result in wide fluctuation in peak and trough steady-state drug levels, which is undesirable for drugs with marginal therapeutic indices. Moreover, patient compliance is likely to be poor when patients need to take their medication three to four times daily on chronic basis. Fortunately, these short comings have been circumvented with the introduction of controlled release dosage forms. These dosage forms are capable of controlling the rate of drug delivery, leading to more sustained drug levels and hence therapeutic action.

Hydrophillic matrix systems are among the most commonly used means for oral controlled drug delivery as they can reproduce a desirable drug profile and are cost effective. The primary mechanism of drug release from hydrophilic matrices occurs when the polymer swells on contact with the aqueous medium to form a gel layer on the surface of the system. The drug then releases by dissolution, diffusion and/or erosion.

TERMINOLOGY

A list of important terms that describe different modified release dosage forms are defined below.

Modified release dosage forms (MRDF)

Defined as those dosage forms whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms.

Controlled release (CR)

The drug is released at a constant (zero order) rate and the drug concentration obtained after administration is invariant with time.

Delayed release

The drug is released at a time other than immediately after administration.

Extended release (ER)

Slow release of the drug so that plasma concentrations are maintained at a therapeutic level for a prolonged period of time (usually between 8 and 12 hours).

Prolonged release

The drug is provided for absorption over a longer period of time than from a conventional dosage form. However, there is an implication that onset is delayed because of an overall slower release rate from the dosage form.

Repeat action

Indicates that an individual dose is released fairly soon after administration, and second or third doses are subsequently released at intermittent intervals.

Sustained release (SR)

The drug is released slowly at a rate governed by the delivery system.[1]

ZERO ORDER DELIVERY

Zero order, or constant rate release of drug is desirable in order to minimize swings in drug concentration in the blood. In conventional dosage forms rapid increase in concentration is followed by a rapid decrease, and little time is spent inside the so-called therapeutic range, which is bounded below by a minimum effective concentration (MEC) and above by a minimum toxic concentration (MTC). Frequent repetitive dosing is required to maintain concentration within these limits, and compliance and control are difficult [2].

Dosage forms that prolong release can maintain drug concentration within the therapeutic range for extended periods and minimize episodes of underexposure or toxicity. A well designed system displays a narrow, predictable residence time distribution in the gastrointestinal (GI) tract, and releases drug by a controlled mechanism. Zero order release leads, in principle, to the best control of plasma concentration. Such control leads to constant drug effect, provided the drug's pharmacokinetic and pharmacodynamic properties, including absorption, distribution, metabolism, and excretion (ADME), and its pharmacodynamic properties relating plasma concentration to drug effect, are stationary.

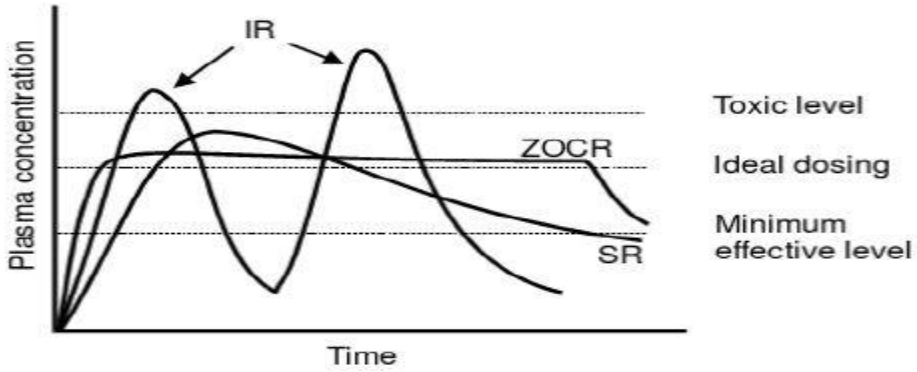

Fig.1 Diagram shows characteristic representation of plasma concentrations of a conventional immediate relese dosage form (IR), a sustained release dosage form (SR) and an idealized zero-order controlled release (ZOCR) dosage form (in combination with a start-up dose).

Zero order oral drug release can be achieved, in principle, by surrounding a core tablet with a membrane that is permeable to both drug and water, as illustrated in. After swallowing, the core becomes hydrated, and drug dissolves until it reaches its saturation concentration or solubility. The core serves as a saturated reservoir of drug. Drug release proceeds by partitioning from the reservoir into the membrane, followed by diffusion across the membrane into the gastrointestinal fluid. So long as saturation is maintained in the core, there will be a stationary concentration gradient across the membrane, and release will proceed at constant rate. Eventually, the dissolved drug's concentration in the core falls below saturation, reducing the concentration gradient and hence the release rate, which decays to zero. If the membrane consists of a water-soluble polymer of high molecular weight, then it will initially swell into a gel, through which drug diffuses. The thickness of the gel layer initially increases with time due to swelling, but ultimately it decreases due to disentanglement and dissolution of polymer chains. At intermediate times, the gel layer may be of approximately constant thickness, and release occurs at a relatively constant rate [2].

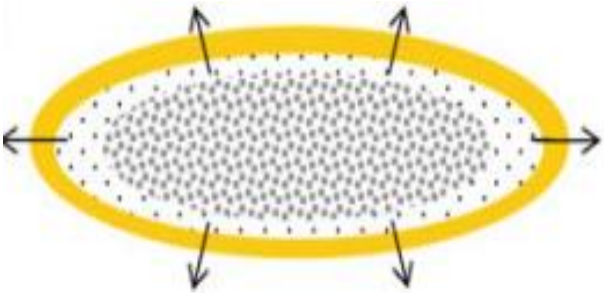

Fig.2 Membrane diffusion controlled release. Drug in core (granulated pattern) dissolves to form saturated solution (dilute dots). Drug then diffuses across membrane (thin tipped arrows). Zero order release persists as long as there is sufficient drug in core to form saturated solution.[2]

MATERIALS AND METHODS

Ibrutinib Procured From Hetero Pharmaceuticals Limited, Hyderabad. Provided by SURA LABS, Dilsukhnagar, Hyderabad. Guar gum from Arvind Remedies Ltd, Tamil nadu, India. Karaya gum from SD Fine Chem. Ltd. (Mumbai, India), Acacia from Yarrow chemicals(Mumbai,India), Lactose from Chemdyes Corporation (Ahmedabad, India), Magnesium stearate from Shakti Chemicals (Mehsana, India), Aerosil from Kerry laboratories

Methodology

Characterization of Ibrutinib

Organoleptic properties

Take a small quantity of sample and spread it on the white paper and examine it visually for color, odour and texture.

Determination of Ibrutinib Melting point

The melting point of Ibrutinib was determined by capillary tube method according to the USP. A sufficient quantity of Ibrutinib powder was introduced into the

capillary tube to give a compact column of 4-6 mm in height. The tube was introduced in electrical melting point apparatus and the temperature was raised. The melting point was recorded, which is the temperature at which the last solid particle of Ibrutinib in the tube passed into liquid phase**.**

Determination of Ibrutinib Solubility

Determination of solubility of drug by visual observation. An excess quantity of Ibrutinib was taken separately and adds in 10 ml of different solutions. These solutions were shaken well for few minutes. Then the solubility was observed and observations are shown in the Table.

Formulation development of Tablets

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 1. The tablets were prepared as per the procedure given below and aim is to prolong the release of Ibrutinib. Total weight of the tablet was considered as 300mg.

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.

Table 1: Formulation composition for tablets

INGREDIENTS	FORMULATION CHART								
	I1	**I2**	**I3**	**I4**	**I5**	**I6**	**I7**	**I8**	**I9**
Ibrutinib	140	140	140	140	140	140	140	140	140
Guar gum	30	60	90	-	-	-	-	-	-
Karaya gum	-	-	-	30	60	90	-	-	-
Acacia	-	-	-	-	-	-	30	60	90
Lactose	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Magnesium stearate	6	6	6	6	6	6	6	6	6
Aerosil	5	5	5	5	5	5	5	5	5
Total Weight	300	300	300	300	300	300	300	300	300

All the quantities were in mg

RESULTS & DISCUSSION

Organoleptic properties

Table 2: Organoleptic properties

S NO.	Properties	Results
1	State	Solid
2	Colour	White
3	Odour	Odourless
4	Melting point	146-148 °C

Solubility studies

Table 3: Solubility studies of drug in different solvents

S NO.	Solvents	Solubility of Ibrutinib
1	Methanol	Soluble
2	Acetonitrile	Sparingly soluble
3	DMSO	Slightly soluble

The present study was aimed to develop extended release tablets of Ibrutinib using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Analytical Method

Graphs of Ibrutinib were taken in 0.1N HCl and in pH 6.8 phosphate buffer at 280 nm and 283 nm respectively.

Table 4: Observations for graph of Ibrutinib in 0.1N HCl (280 nm)

Conc. [µg/ml]	Absorbance
0	0
5	0.126
10	0.241
15	0.345
20	0.451
25	0.562

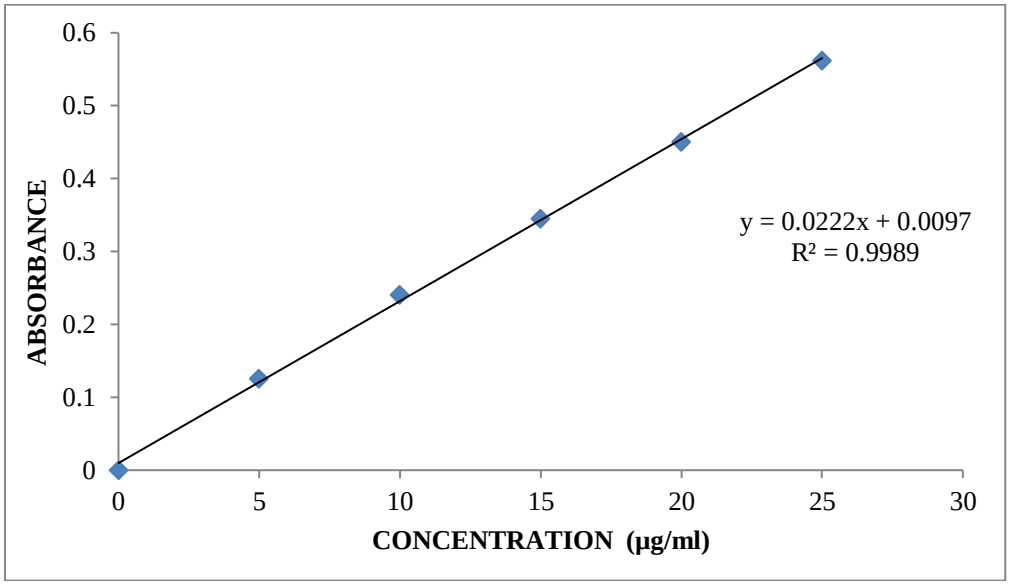

Figure 3: Standard graph of Ibrutinib in 0.1N HCl

Table 5: Observations for graph of Ibrutinib in pH 6.8 phosphate buffer (283nm)

Concentration [µg/ml]	Absorbance
0	0
5	0.154
10	0.295
15	0.421
20	0.564
25	0.691

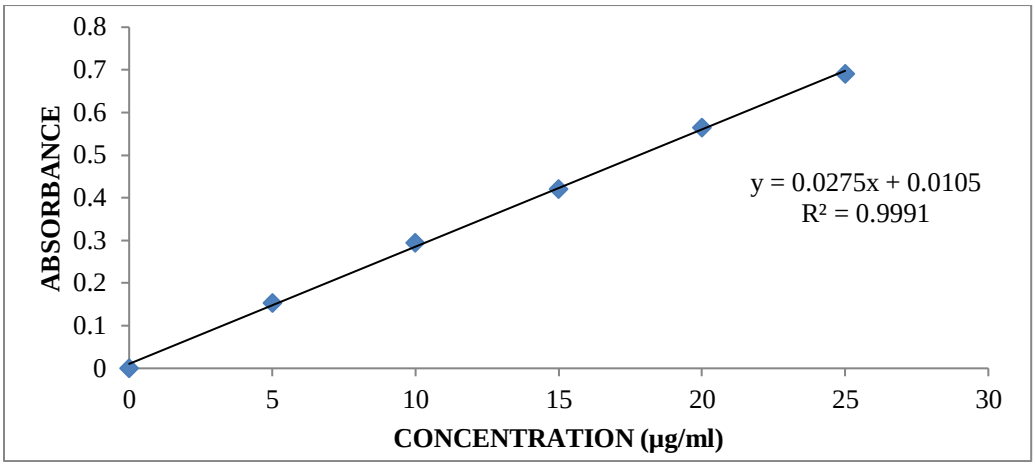

Figure 4: Standard graph of Ibrutinib pH 6.8 phosphate buffer (283s nm)

Preformulation parameters of powder blend

Table 6: Pre-formulation parameters of Core blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
I1	29.35	0.538	0.649	17.10	1.20
I2	30.30	0.546	0.665	17.89	1.21
I3	28.32	0.576	0.672	14.28	1.16
I4	29.98	0.524	0.657	20.24	1.25
I5	29.66	0.564	0.677	16.69	1.20
I6	29.98	0.536	0.635	15.59	1.18
I7	30.32	0.576	0.650	11.38	1.12
I8	27.33	0.547	0.657	16.74	1.20
I9	30.62	0.567	0.678	16.37	1.19

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.524 to 0.576 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.635 to 0.678 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 17 which show that the powder has good flow properties. All the formulations has shown the hausner ratio below 1.20 indicating the powder has good flow properties.

Quality Control Parameters For tablets

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet.

Table 7. *In vitro* quality control parameters for tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)
I1	299.25	4.9	0.31	3.59	97.61
I2	297.52	4.4	0.46	3.81	98.27
I3	299.10	4.6	0.29	3.93	96.92

I4	300.01	4.0	0.34	3.64	99.79
I5	297.96	4.7	0.47	3.50	98.64
I6	298.58	5.1	0.50	3.99	95.27
I7	299.72	4.8	0.29	3.64	98.46
I8	299.18	4.3	0.36	3.28	97.92
I9	298.34	5.0	0.40	3.49	99.05

Weight variation test

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 7. The average weight of the tablet is approximately in range of 297.52 to 300.01 mg, so the permissible limit is ±7.5% (>300 mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test

Hardness of the three tablets of each batch was checked by using Pfizer hardness tester and the data's were shown in Table 7. The results showed that the hardness of the tablets is in range of 4.0 to 5.1 kg/cm^2, which was within IP limits.

Thickness

Thickness of three tablets of each batch was checked by using Micrometer and data shown in Table-7. The result showed that thickness of the tablet is raging from 3.28 to 3.99 mm.

Friability

Tablets of each batch were evaluated for percentage friability and the data were shown in the Table 7. The average friability of all the formulations was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Drug content

Drug content studies were performed for the prepared formulations. From the drug content studies it was concluded that all the formulations were showing the % drug content values within 95.27 - 99.79 %.
All the parameters such as Weight Variation, Friability, Hardness, Thickness and Drug Content were found to be within limits.

In Vitro Drug Release Studies

Table 8: Dissolution Data of Ibrutinib Tablets

Time (HRS)	% of Drug release								
	I1	**I2**	**I3**	**I4**	**I5**	**I6**	**I7**	**I8**	**I9**
0	0	0	0	0	0	0	0	0	0
0.5	14.21	12.12	16.45	18.16	14.90	11.38	17.76	10.16	08.92
1	24.53	18.26	23.32	26.20	24.15	16.43	21.89	15.44	13.68
2	38.90	26.35	30.50	32.54	31.21	28.35	28.24	22.78	18.75
3	45.96	32.20	35.15	45.20	38.23	34.89	33.32	26.25	21.82
4	49.14	37.15	42.25	58.46	45.60	39.39	37.75	30.40	26.35
5	53.85	44.64	51.78	66.44	53.18	48.31	42.09	37.60	32.11
6	57.93	48.56	59.57	74.01	56.74	54.15	49.16	40.67	36.82

7	64.10	53.95	64.79	84.57	64.05	62.67	53.36	48.26	41.29
8	71.21	60.71	70.27	95.24	78.93	68.02	56.12	54.67	46.57
9	86.72	72.96	75.64		85.26	76.15	64.78	57.42	53.92
10	98.14	81.50	77.87		97.30	80.45	75.79	64.21	57.43
11		96.36	82.36			88.50	87.31	78.36	61.50
12			98.87			99.14	96.65	83.40	76.41

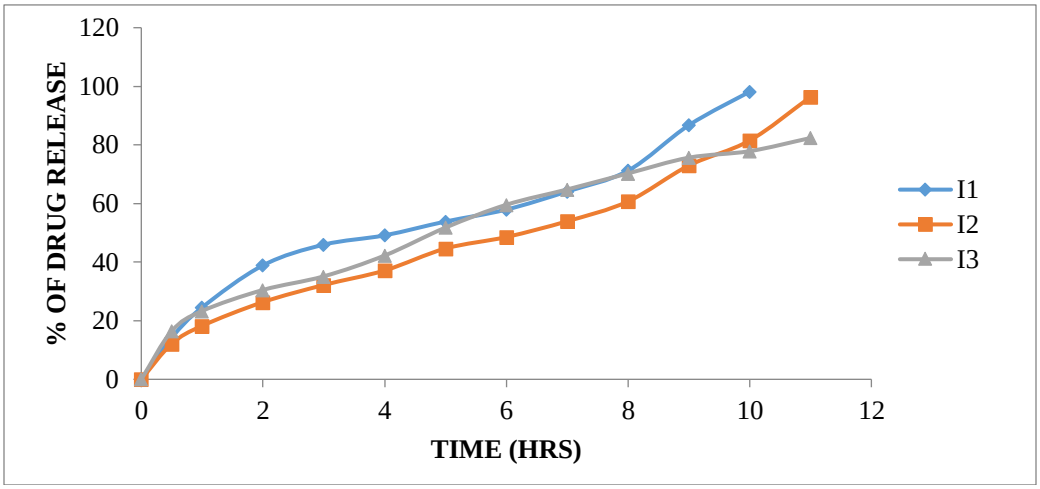

Fig 5: Dissolution profile of Ibrutinib (I1, I2, I3 formulations)

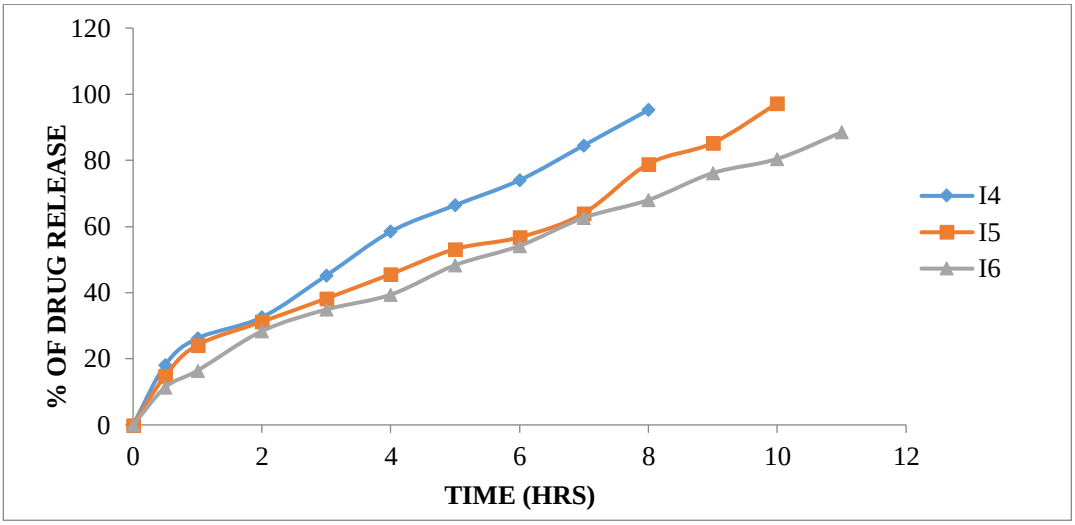

Fig 6: Dissolution profile of Ibrutinib (I4, I5, I6 formulations)

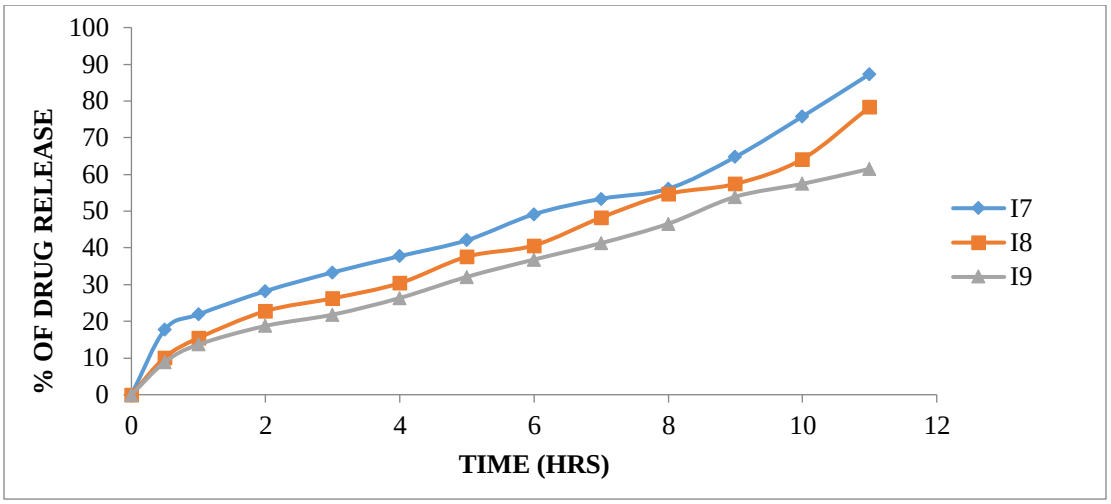

Fig 7: Dissolution profile of Ibrutinib (I7, I8, I9 formulations)

From the dissolution data it was evident that the formulations prepared with Guar gum as polymer were retard the drug release up to desired time period i.e., 12 hours.

Formulations prepared with Karaya gum retarded the drug release in the concentration of 90 mg (I6 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 99.14 % in 12 hours with good drug release.

The Formulation Containing Acacia in 30 mg Concentration Showed good retarding nature with required drug release in 12 hours i.e., 96.65 %.

From the above results it was evident that the formulation I6 is best formulation with desired drug release pattern extended up to 12 hours.

Application of Release Rate Kinetics to Dissolution Data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Table 9: Release kinetics data for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt 1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
11.38	0.5	0.707	1.056	-0.301	1.948	22.760	0.0879	-0.944	88.62	4.642	4.458	0.183
16.43	1	1.000	1.216	0.000	1.922	16.430	0.0609	-0.784	83.57	4.642	4.372	0.270
28.35	2	1.414	1.453	0.301	1.855	14.175	0.0353	-0.547	71.65	4.642	4.153	0.488
34.89	3	1.732	1.543	0.477	1.814	11.630	0.0287	-0.457	65.11	4.642	4.023	0.619

39.39	4	2.000	1.595	0.602	1.783	9.848	0.0254	-0.405	60.61	4.642	3.928	0.713
48.31	5	2.236	1.684	0.699	1.713	9.662	0.0207	-0.316	51.69	4.642	3.725	0.917
54.15	6	2.449	1.734	0.778	1.661	9.025	0.0185	-0.266	45.85	4.642	3.579	1.062
62.67	7	2.646	1.797	0.845	1.572	8.953	0.0160	-0.203	37.33	4.642	3.342	1.299
68.02	8	2.828	1.833	0.903	1.505	8.503	0.0147	-0.167	31.98	4.642	3.174	1.467
76.15	9	3.000	1.882	0.954	1.377	8.461	0.0131	-0.118	23.85	4.642	2.878	1.763
80.45	10	3.162	1.906	1.000	1.291	8.045	0.0124	-0.094	19.55	4.642	2.694	1.948
88.5	11	3.317	1.947	1.041	1.061	8.045	0.0113	-0.053	11.5	4.642	2.257	2.384
99.14	12	3.464	1.996	1.079	-0.066	8.262	0.0101	-0.004	0.86	4.642	0.951	3.691

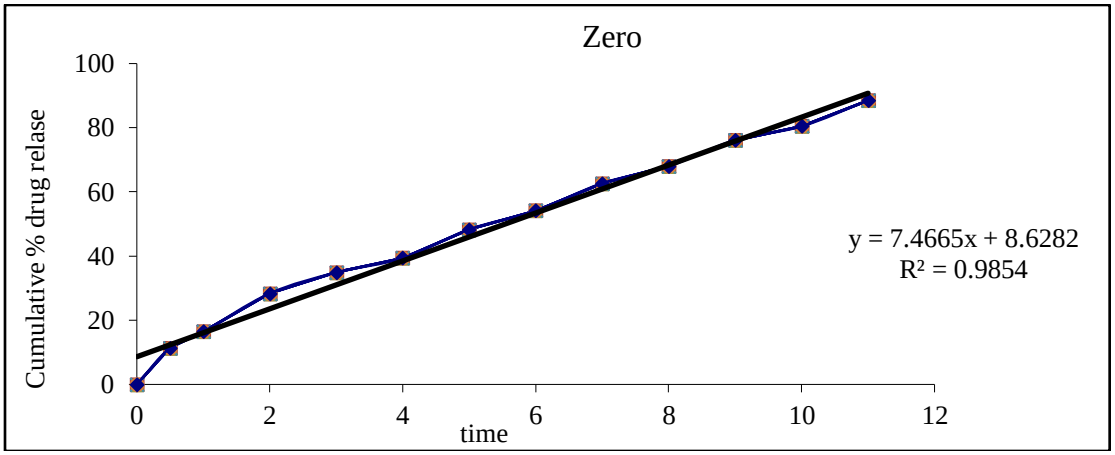

Fig 8 : Zero order release kinetics graph

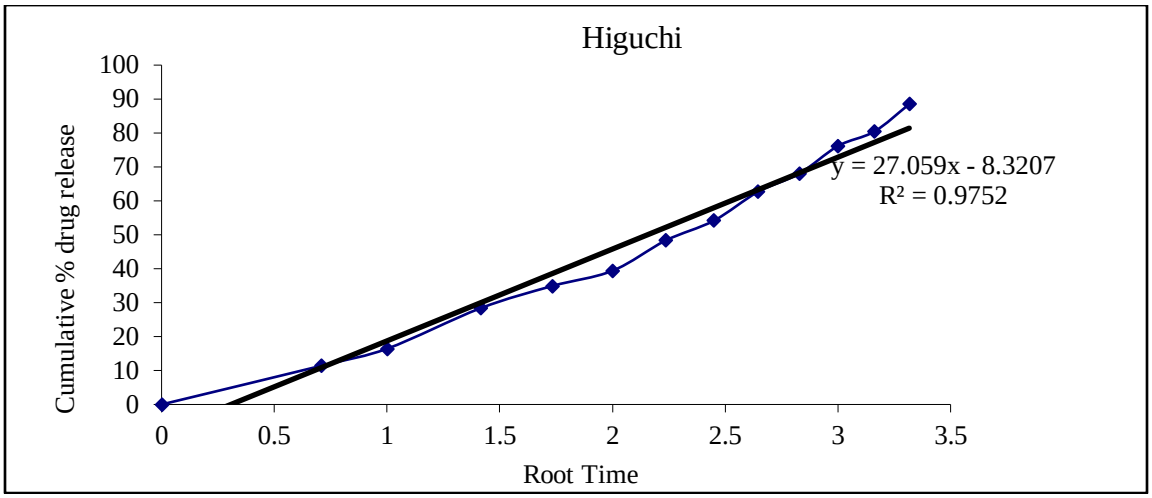

Fig 9: Higuchi release kinetics graph

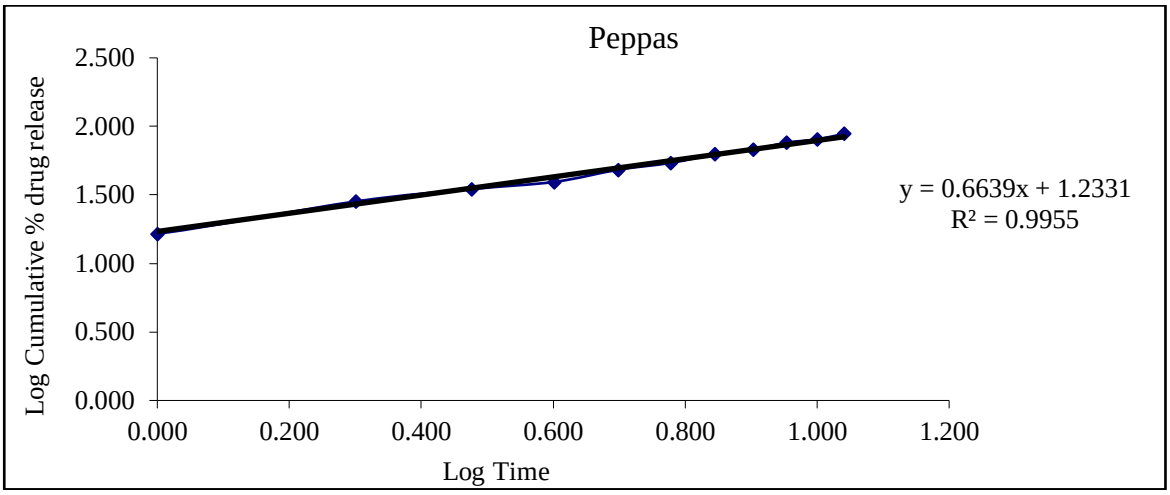

Fig 10: Kars mayer peppas graph

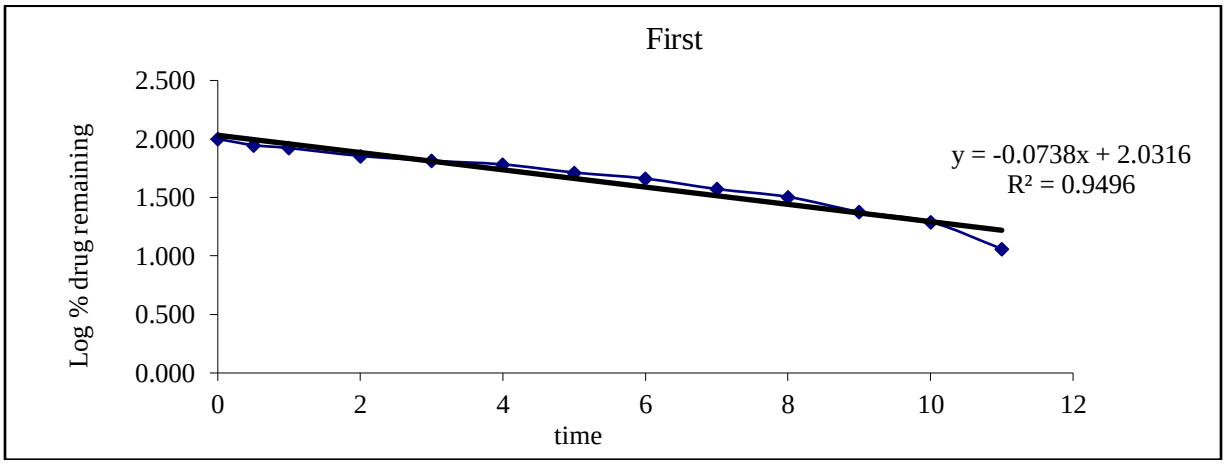

Fig 11: First order release kinetics graph

From the above graphs it was evident that the formulation I6 was followed Kars Mayer peppas release kinetics.

Table 10: kinetics Correlation coefficient values

Release Kinetics	Correlation coefficient values
Zero order release kinetics	$R^2 = 0.985$
Higuchi release kinetics	$R^2 = 0.975$
Peppas release kinetics	$R^2 = 0.995$
First order release kinetics	$R^2 = 0.949$

Drug – Excipient compatibility studies

Fourier Transform-Infrared Spectroscopy

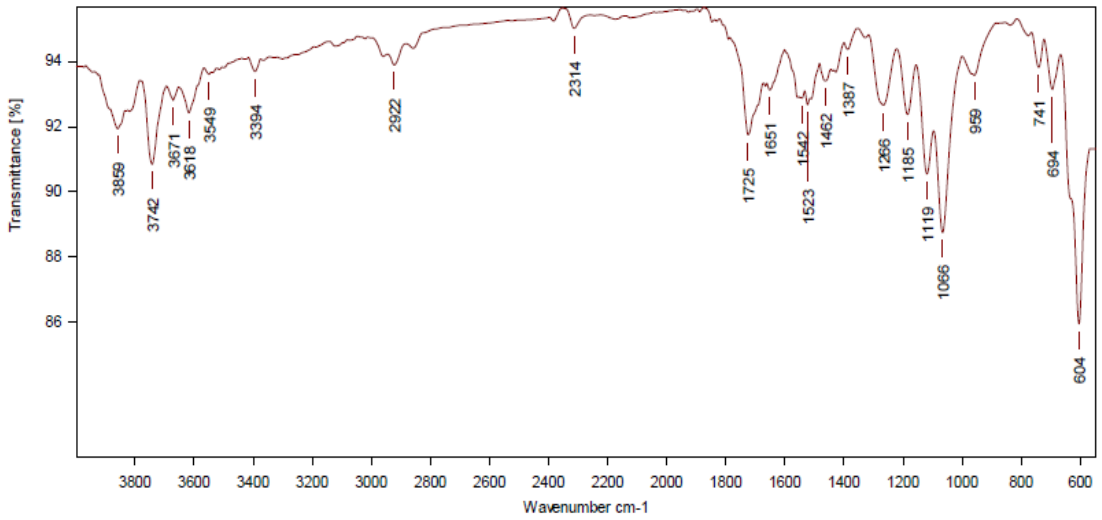

Figure 12: FT-TR Spectrum of Ibrutinib pure drug

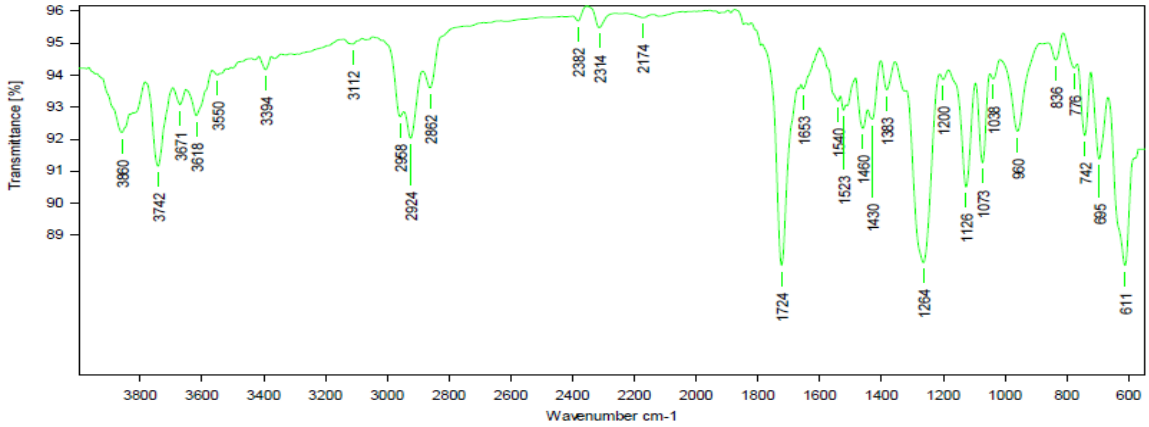

Figure 13: FT-IR Spectrum of Optimised Formulation

From the above studies it was found that there was no shifting in the major peaks which indicated that there were no significant interactions occurred between the Ibrutinib and excipients used in the preparation of different Ibrutinib extended release tablets formulations. Therefore the drug and excipients are compatible to form stable.

Formulations under study The FTIR spectra of extended release tablets and physical mixture used for optimized formulation were obtained and these are depicted in above figures. From the FTIR data it was evident that the drug and excipients does not have any interactions. Hence they were compatible.

CONCLUSION

The present study was carried out on Ibrutinib. The main aim of this study is to extend the drug release up to 12 hrs. Drug wavelength and calibration curve was developed in 0.1N HCL and pH 6.8 Phosphate buffer.

The drug and excipient compatibility studies were shown good compatibility between drug and excipients. Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose, bulk density, tapped density, compressibility index and hausner ratio powder has good flow properties.

Post compression studies like Weight variation, Hardness, thickness, friability, drug content was determined within IP limits. From the dissolution data it was evident that the formulation I6 is best formulation with desired drug release pattern extended up to 12 hours. The formulation I6 was followed Kars Mayer peppas release kinetics.

Future Scope

Further if the formulation is to be taken for generic market, since pilot B.E studies is showing passing results as per the limits set by ICH guidelines. The Pilot scale batches and validation will have to be taken at the manufacturing plant to optimize the processing parameters. Pivotal B.E studies in fed, fasted condition and steady state studies will have to be performed so as to register the product as generics. Bioequivalence will be Perform on the selected formulation in human subjects in fasting condition. And will perform Pharmacoeconomics of the developed formulation for the cost comparison.

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