AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

Formulation and Evaluation of Sustained Release Matrix Tablets of Ibrutinib

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ABSTRACT

The present study focuses on developing sustained release matrix tablets of Ibrutinib aiming to increase the therapeutic efficacy, reduce the frequency of administration and to improve the patient compliance. Sustained release matrix tablets of Ibrutinib, were developed by using different drug polymer ratios HPMC phthalate, Eudragit L 100, Eudragit S 100 as matrix former. All lubricated formulations were compressed by direct compression and by wet granulation method. Compressed tablets were evaluated for uniformity of weight, content of active ingredient, friability, hardness, thickness, *in-vitro* dissolution, and swelling index. All the formulation showed compliance with pharmacopoeial standards. Among the different formulation, B8 showed sustained release of drug for 12 hours with 86.55% release. The selected formulation (B8) was subjected to stability studies for three months at 25°C/60% RH, 30°C/65% RH and 40°C/75% RH and showed stability with respect to release pattern and all physical parameters. The regression coefficient value of Higuchi plot was found to be 0.9925 that showed that drug was released by diffusion mechanism. The slope value of korsmeyer-peppas equation was found to be 0.5062 which indicating that drug was released by non-fickian release mechanism. The R^2 value for Hixson Crowell plot was found to be 0.9919 which indicates that drug release was limited by drug particle dissolution rate and erosion of the polymer matrix. Thus, drug in combination with Eudragit S 100 were found to be effective in retarding the release of Ibrutinib.

Keywords: Ibrutinib, sustained release, matrix tablet, HPMC phthalate, Eudragit L 100, Eudragit S 100.

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Received 04 July 2017, Accepted 15 July 2017

Please cite this article as: Palanisamy P *et al*., Formulation and Evaluation of Sustained Release Matrix Tablets of Ibrutinib . American Journal of PharmTech Research 2017.

INTRODUCTION

The diffusion system where the drug is uniformly distributed (dispersed / dissolved) throughout the solid matrix and release of the drug is controlled or sustained either by incorporating hydrophilic or hydrophobic filler within the matrix or by coating the drug matrix with a swellable or non-swellable polymer film[1-2].

Acquired Immuno Deficiency Syndrome (AIDS), which threatens to be a major cause a great plague in the present generation. It is very crucial for the success of AIDS therapy to maintain the therapeutic drug concentration consistently above its target antiretroviral concentration throughout the course of the treatment.

Ibrutinib, a novel anti-HIV compound approved for the clinical use in treatment of AIDS either alone or in combination with other antiviral agents. Ibrutinib is water insoluble and soluble at all pH ranges and absorbed through the stomach and so sustained release tablet is better approach then the conventional dosage form[3].

Ibrutinib, a novel oral tyrosine kinase inhibitor that irreversibly binds and inhibits tyrosine-protein kinase BTK (Bruton tyrosine kinase). BTK has been found to be important in the function of B-cell receptor signaling and therefore in the maintenance and expansion of various B-cell malignancies including chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL). Targeting BTK with Ibrutinib has been found to be an effective strategy in treating these malignancies. Sustained release delivery of drug is desired to maintain anti-AIDS effect and avoiding severe side effects[4].

MATERIALS AND METHOD

Ibrutinib was gifted by Max wel Pharmaceuticals, Mumbai, HPMC phthalate , Eudragit L 100, Eudragit S 100 was gifted by Merck Limited, Bangalore, DCP (A-Tab), Lactose, PVP K30, IPA, Talc, Mg Stearate and Aerosil Asahi Kasei – Japan / Signet chemical, Mumbai.

Preparation of Standard graph of Ibrutinib[5]

Standard curve of Ibrutinib was prepared by dissolving 100mg of pure drug in 100ml of purified water in 100ml of standard volumetric flask. Then dilution was made by pipetting out 10ml from this solution and made upto 100ml using purified water and again dilution was made by pipetting out 10 ml from the above solution and made upto 100ml using purified water which gives 10mcg/ml concentration and 0.469 absorbance. The absorbance was given in the Fig. No. 1.

Compatibility Study[6]

Compatibility studies were performed for physical observation and confirmed by using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied. The characteristic absorption peaks of Ibrutinib were obtained at following wavelengths.

Preformulation Studies[7-8]

Evaluation of Granules

Bulk Density

The bulk density for the formulated blend was carried out for all formulations and found in the range of 0.37 – 0.50 g/ml. Results were shown in Table No. 2.

Tapped density

The tapped densities for the formulated blend was carried out for all formulations and found in the range of 0.45 – 0.62 g/ml. Results were shown in Table No.2.

Angle of repose

The angles of repose for the formulated blends were carried out and the results were shown in Table No.2. It concluded that all the formulations blend was found in the range of $27^0.70´$ to $39^0.8´$**.**

Compressibility index

Compressibility index was carried out and the results were shown in Table No.2. It were found between 11.1% to 21.2 % indicating the powder blend have the required flow property for compression except for batch B1 that is having %compressibility 27.2%.

Porosity

Porosity was carried out and the results were shown in Table No.2. It were found between 12% to 23 % indicating the powder blend have the required flow property for compression except for batch B1 that is having % porosity 28%.

Hausner's Ratio

Hausner's Ratio was carried out and the results were shown in Table No.2. It were found between 11.1% to 21.2 % indicating the powder blend have the required flow property for compression except for batch B2 that is having Hausner's ratio 27.2%.

Table 1: Formulation Chart of Sustained Release Matrix Tablets of Ibrutinib

S.No	Ingredients	B1	B2	B3	B4	B5	B6	B7	B8
1	Ibrutinib	420	420	420	420	420	420	420	420
2	HPMC phthalate	60	60	75	-	-	-	-	-
3	Eudragit L 100	-	-	-	60	60	90	-	-
4	Eudragit S 100	-	-	-	-	-	-	60	75
5	DCP (A-Tab)	155	150	135	140	-	-	-	-

6	Lactose	-	-	-	-	140	110	130	125
7	PVP K30	-	-	-	25	25	25	25	25
8	IPA				Q.S.	Q.S.	Q.S.	Q.S.	Q.S
9	Talc	10	10	10	-	-	-	-	-
10	Mg Stearate	5	5	5	5	5	5	5	5
11	Aerosil	-	5	5	-	-	-	-	-

All quantities are in mg and wt. of tablet 650 mg

EVALUATION OF TABLETS[9-10]

Weight Variation

The percentage weight variations for all formulations were tabulated in Table No. 3. All the formulated tablets passed weight variation test except formulation B1 as the % weight variation was within the pharmacopoeial limits of ±5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness

The thickness was determined for formulated tablets and tabulated in Table No. 3. Tablets mean thickness (n=3) were uniform in B1 to B8 formulations and were found to be in the range of 3.74mm to 3.90mm for batches B1 to Batch B3 and 4.14mm to 5.11mm for batches B4 to B8 and the coated tablets having thickness 5.13mm to 5.18 mm.

Hardness

The measured hardness of tablets of each batch ranged between 130 – 170N for formulation (B1-B3) and 230 - 250N for formulation (B4-B8) were tabulated in Table No.3. This ensures good handling characteristics of all batches.

Friability

The values of friability test were tabulated in Table No.3. The % friability was less than 1% in all the formulations except formulation B4 ensuring that the tablets were mechanically stable.

Content Uniformity

The percentage of drug content for B1 to B8 was found to be between 97.85% and 99.53% of Ibrutinib, it complies with official specifications. The results were shown in Table No.3.

***In-vitro* Dissolution Study and Kinetic modeling of drug release**[11-13]

All the eight formulation of prepared matrix tablets of Ibrutinib were subjected to in-vitro release studies except batch B1 and B4 these studies were carried out using Electrolab TDT 08L dissolution apparatus (USP). The dissolution medium consisted of 900 ml of purified water for 12 hrs.

The results obtained in in-vitro release studies were plotted in different model of data treatment as follows:

1. Cumulative percent drug released vs. time (zero order rate kinetics)
2. Log cumulative percent drug retained vs. time (First Order rate Kinetics)
3. Log Cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)
4. Log of cumulative % release Vs. log time (Peppas Exponential Equation)
5. (Percentage retained)$^{1/3}$ Vs. time (Hixson –Crowell Erosion Equation)

This model is widely used when the release mechanism is not well know or when more than one type of release phenomenon was involved. The 'n' values can be used to characterize diffusion release mechanism as

'n'	**Mechanism**
0.5	Fickian diffusion
0.5<n<1	Non- fickian diffusion
1	Class II transport

Thus, it may be concluded that the drug release from sustained release matrix tablet of Ibrutinib is best explained by Higuchi model (R^2=0.9925) and the release of drug was governed by diffusion mechanism.

Swelling Study[14-15]

Swelling study was performed on all the batches (B5 to B8) for 12 hrs. The results of swelling index were shown in Table No. 7. Swelling index against time (hrs.) was plotted in Figure 7.

Swelling index was calculated with respect to time. Swelling index increased with time as the weight gain by the tablet was increased proportionally with the rate of hydration. The swelling index of the Batch B4 to B6 containing Eudragit L 100 was less as compare to the Batch B7 and B8 containing Eudragit S 100; it might be due to the high viscosity of Eudragit S 100than Eudragit L 100.

In case of batch B5 to B6 containing Eudragit L 100 in concentration of 12% and 18% respectively, showed considerable swelling and achieve 69.2% and 77.3% swelling in 4 hrs. and afterwards weight of the tablet decreases due to erosion of the polymer matrix.

The Batch B7 and B8 containing Eudragit S 100 in 12% and 15% concentration initially swell slowly but achieve maximum swelling and achieve 92.5% and 96.3% swelling in 4 hrs. and afterwards weight of the tablet decreases due to erosion of the polymer matrix.

In the present study, the higher swelling index was found for tablets of batch B7 and batch B8 containing Eudragit S 100 having nominal viscosity of more than 1, 00,000 cps. Thus, the viscosity of the polymer had major influence on swelling process and matrix integrity hence from the above results it can be concluded that linear relationship exists between swelling process and viscosity of polymer.

Stability Studies[16-17]

Sustained release matrix tablets of Ibrutinib formulated in the present study were subjected to accelerated stability studies. Stability studies of the prepared formulations were performed at ambient temperature and humidity conditions at i.e. 25°C/60%RH, 30°C/65%RH, 40°C/75%RH for 3 months and analyzed after one month and three months for its appearance, hardness, friability, drug content and in-vitro release.

RESULTS AND DISCUSSION

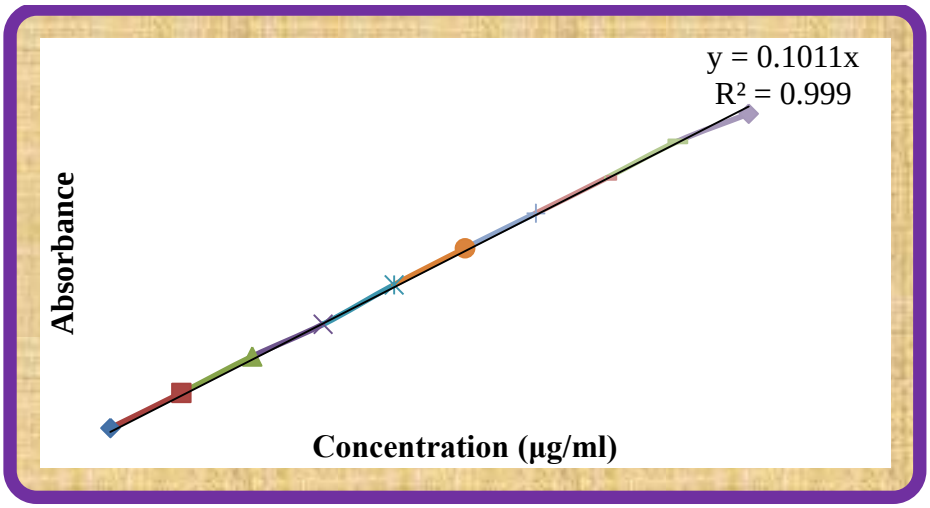

Figure 1: Absorbance of Standard curve of Ibrutinib in Purified Water at 260nm

FT-IR SPECTROSCOPY:

The result of FT-IR study for Ibrutinib and their excipients are shown in Figure 2 -6.

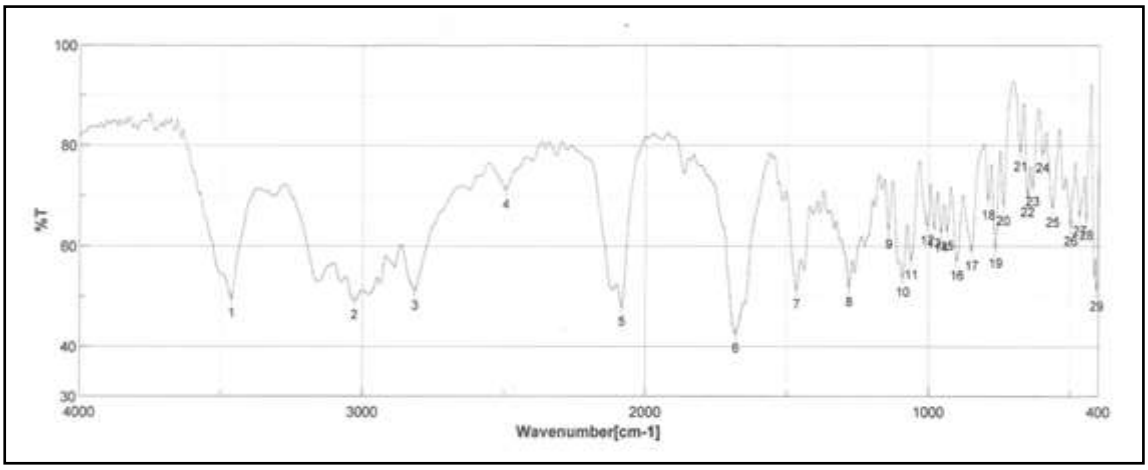

Figure 2: I.R. Spectra of Ibrutinib

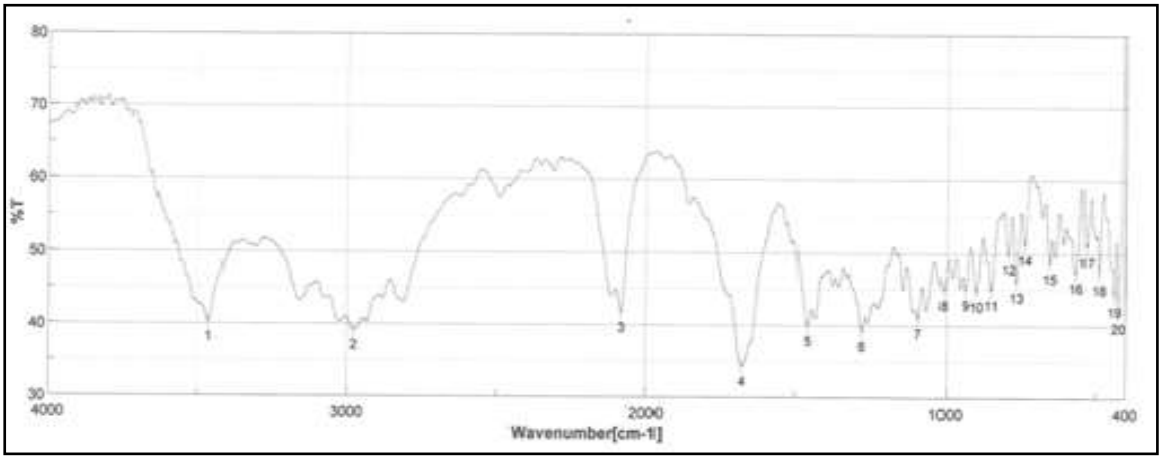

Figure 3: I.R. Spectra of Ibrutinib + HPMC phthalate

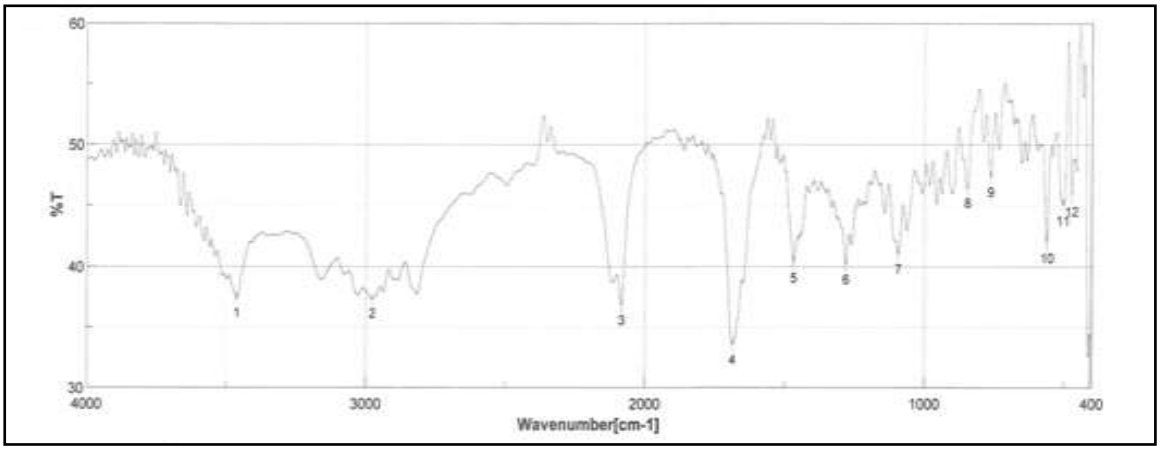

Figure 4 :I.R. Spectra of Ibrutinib + Eudragit L 100

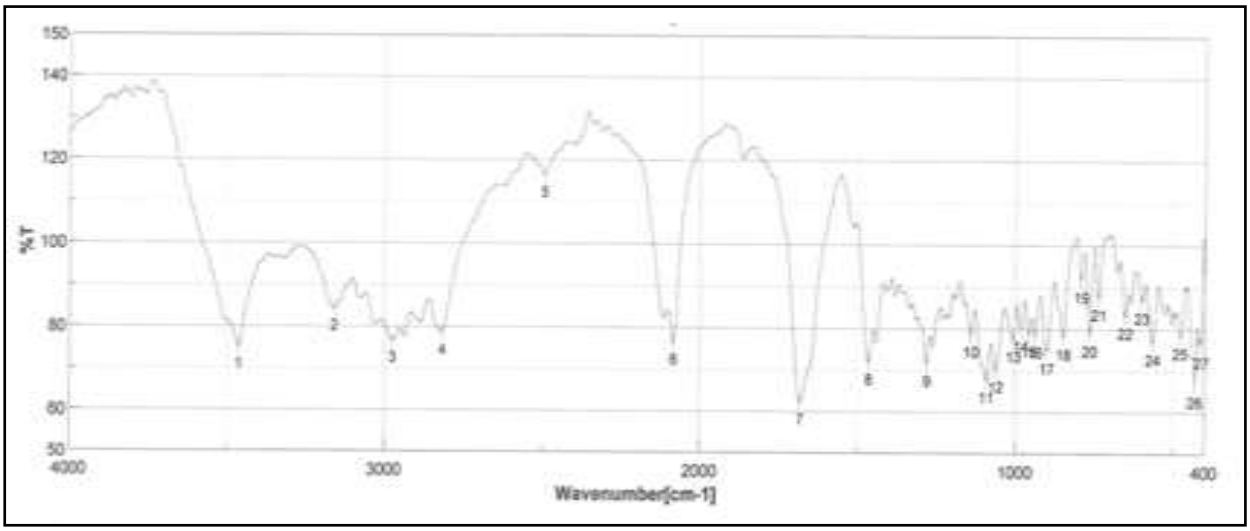

Figure 5: I.R. Spectra of Ibrutinib + Eudragit S 100

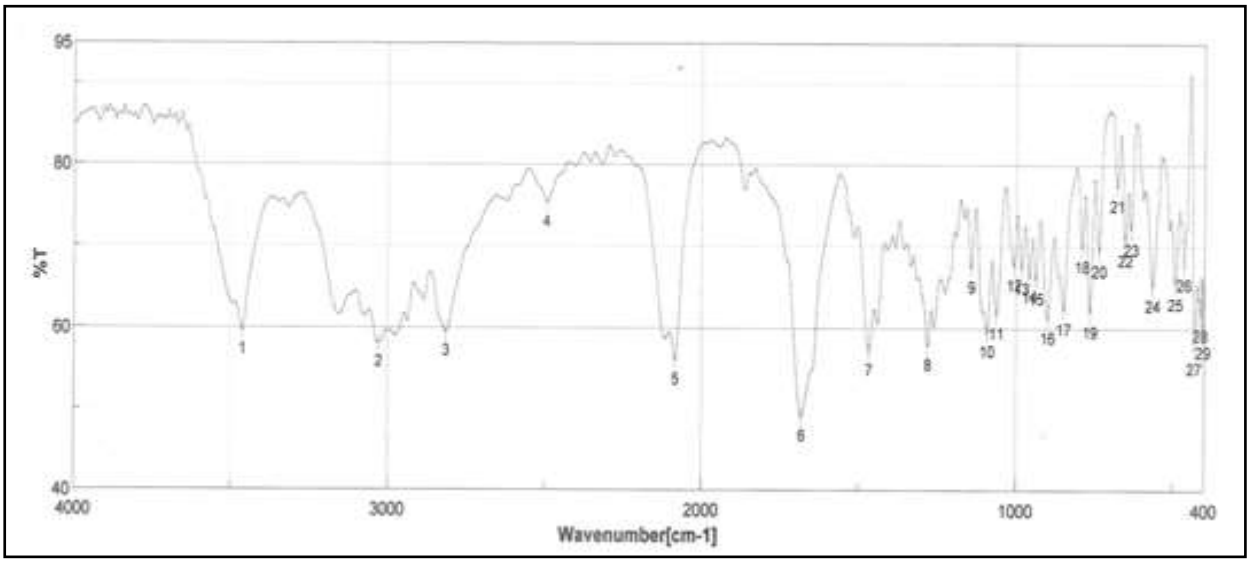

Figure 6: I.R. Spectra of Ibrutinib + PVP K30

Table 2: Characterization of Trial Blends

B. NO	**Bulk Density (g/ml)**	**Tapped Density (g/ml)**	**Compressibility Index (%)**	**Hausner's Ratio**	**Porosity (%)**	**Angle of repose (θ)**	**Loss on Drying (%)**
B1	0.40	0.55	27.2	1.37	28	39°.8′	-
B2	0.47	0.55	14.5	1.17	15	32°.8′	-
B3	0.50	0.62	20.0	1.25	20	32°.4′	-
B4	0.37	0.47	21.2	1.27	23	28°.3′	2.26
B5	0.38	0.43	11.6	1.13	12	28°.7′	2.31
B6	0.40	0.45	11.11	1.12	12	29°.3′	2.08
B7	0.38	0.47	19.1	1.23	20	27°.7′	2.11
B8	0.38	0.45	15.5	1.18	16	27°.9′	2.17

Table 3: Physical parameters of tablets of each batch

B. NO.	Weight Variation (mg)*	Thickness (mm)*	Hardness (N)*	Friability (%)	Drug Content (%)
B1	652.4±25.7	3.90±0.18	149.0±15.09	0.36	-
B2	655.2±3.11	3.82±0.06	151.3±8.96	0.33	99.53
B3	650.3±3.06	3.74±0.09	147.6±8.32	0.10	98.73
B4	651.3±2.7	4.15±0.10	236.6±4.16	1.26	-
B5	651.8±4.62	4.14±0.08	239.6±7.23	0.68	97.85
B6	652.8±2.67	4.14±0.10	235.3±6.11	0.30	99.23
B7	660.6±1.80	4.18±0.13	239.0±4.35	0.10	98.79
B8	650.4±1.9	5.13±0.02	236.3±3.51	0.11	98.72
B8c	651.2±1.15	5.18±0.03	241.6±4.50	-	97.84

*** Each value represents the mean ± standard deviation (n = 3)**

*** B8 = Core Tablet & * B8c = Coated Tablet**

Table 4: Dissolution Profile of batch no. B2 to B8

B. NO.	Cumulative % drug release (hrs.)						
	1	2	4	6	8	10	12
B2	27.72	37.55	52.49	65.69	76.03	85.10	93.10
B3	23.34	28.72	49.65	71.92	38.02	64.93	78.93
B5	37.91	46.83	68.01	86.63	96.85	101.03	-
B6	27.33	38.95	56.06	65.74	79.39	88.43	100.7
B7	31.81	40.73	53.06	69.12	83.10	91.22	98.09
B8	26.06	34.57	45.84	57.13	72.00	81.59	87.30
B8c	25.60	33.75	44.73	56.37	70.80	80.74	86.55

*** B8 = Core Tablet & * B8c = Coated Tablet**

Table 5: Swelling Index of Tablets of Batch B1 to B8

S. No.	Time (hrs.)	Swelling Index (%)							
		B1	B2	B3	B4	B5	B6	B7	B8
1	1	13.6	30.1	33.6	32.5	23.6	32.4	39.6	42.5
2	2	32.4	42.1	51.1	53.2	42.4	48.6	54.1	63.2
3	4	49.2	73.4	84.5	91.3	69.2	77.3	92.5	96.3
4	6	71.3	63.1	80.6	94.8	61.3	67.3	89.6	91.8
5	8	54.2	50.2	72.2	74.4	54.5	59.2	78.2	84.4
6	10	50.3	49.6	64.4	73.3	51.3	53.6	69.4	76.3
7	12	41.2	47.1	61.7	70.6	46.2	49.1	65.7	74.6

Table 6: In-vitro release profile of Ibrutinib sustained release matrix tablets of B8 formulation

Time (hrs)	Root T	Log T	Cum % drug release	Cum % drug retained	Log Cum % drug release	Log Cum % drug retained	(% retained)$^{1\backslash 3}$
1	1	0	26.06	73.94	1.41	1.86	4.19
2	1.414	0.301	34.57	65.43	1.53	1.81	4.02
4	2	0.602	45.84	54.16	1.66	1.73	3.78
6	2.449	0.778	57.13	42.87	1.75	1.63	3.49

8	2.828	0.903	72.00	28.00	1.85	1.44	3.03
10	3.162	1	81.59	18.41	1.91	1.26	2.64
12	3.464	1.079	87.30	12.7	1.94	1.10	2.33

Table 7: Kinetic values obtained from in-vitro released data of formulation B8

Kinetic values obtained from in vitro released data of formulation B8			
Kinetic Model	**Intercept**	**Slope**	**R^2**
Zero-order plot	14.468	6.5765	0.943
First-order plot	1.9809	-0.0685	0.9802
Higuchi plot	-1.2769	25.05	0.9925
Peppas-korsmeyer	1.3771	0.5062	0.9891
Hixson Crowell	4.4221	-0.1692	0.9919

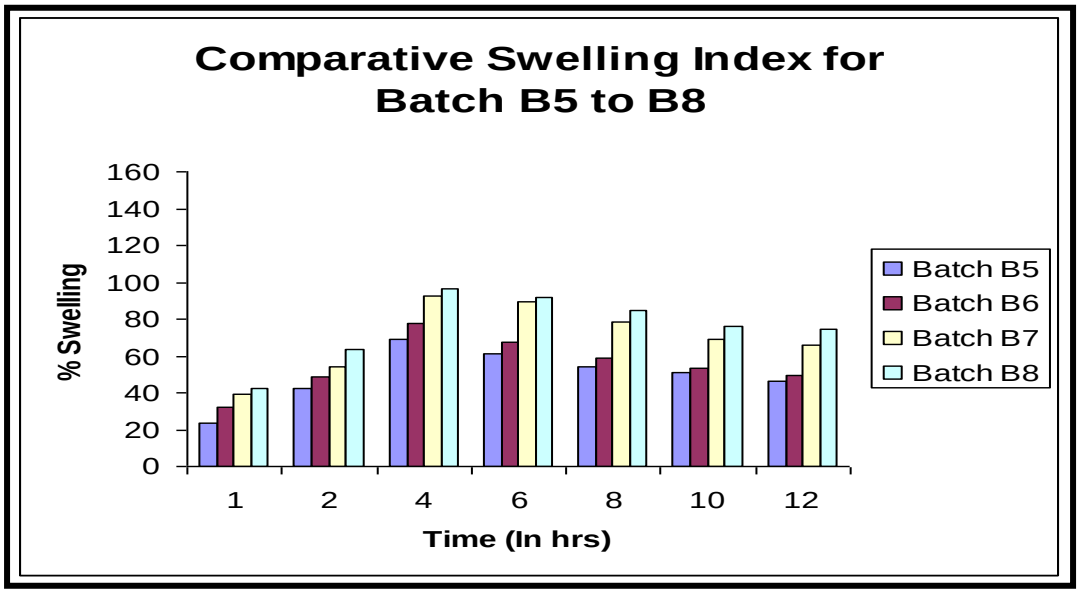

Figure 7: Comparative Swelling Index for Batch B5 TO B8

STABILITY STUDY

Dissolution Profile

S. No.	Time (hrs.)	% cumulative Drug Release					
		After 30 Days			After 90 Days		
		25°C/60%RH	32°C/65%RH	40°C/75%RH	25°C/60%RH	30°C/65%RH	40°C/75%RH
1	1	25.95	25.39	26.24	25.53	25.46	26.16
2	2	34.11	34.24	34.36	34.11	34.35	34.64
3	4	45.06	45.20	45.56	45.06	45.44	44.82
4	6	56.35	56.83	56.53	56.19	56.94	56.27
5	8	70.25	71.17	71.25	70.0	70.75	70.96
6	10	80.92	80.73	80.45	81.12	80.59	80.12
7	12	86.55	87.58	87.84	86.76	87.86	87.86

Drug Content

S. No.	% cumulative Drug Release	
	After 30 Days	After 90 Days

	25°C/60%RH	32°C/65%RH	40°C/75%RH	25°C/60%RH	30°C/65%RH	40°C/75%RH
1.	98.48	99.51	99.31	96.94	97.53	97.80

SUMMARY AND CONCLUSION

The present study was undertaken with the aim of formulating sustained release matrix tablets of Ibrutinib using different polymers and evaluating the tablets by physical characterization, *in-vitro* release kinetics study and stability studies.

Various sustained release matrix tablet formulations of Ibrutinib with various polymers viz, HPMC phthalate, Eudragit L100 and Eudragit S100 in different ratios were formulated by direct compression and by wet granulation technique. Granules were evaluated for Bulk density, Tapped density, Compressibility index, Porosity, Angle of repose, Hausner's ratio before being punched as tablets. Results of the pre-formulation studies for different batches of Ibrutinib prepared using selected excipients, directed for further course of formulation. Observations of physical characterization for all formulations showed that, all of them comply with the specifications of official pharmacopoeias and/or standard references. The formulations were coated with opadry AMB to prevent from moisture contamination.

Results of *in-vitro* release profile study indicated that among all the formulations, B8 was the most promising formulation with 86.55% drug release within 12 hrs. The *in-vitro* release data was plotted for various Kinetic models. The R^2 value for Higuchi plot was determined to be 0.9925 which indicates that the drug release is being governed by diffusion mechanism and the R^2 value for Hixson Crowell plot was determined to be 0.9919 indicating the drug release been limited by drug particle dissolution rate and the erosion rate of the polymer matrix. Slope value of korsmeyer-peppas equation was found to be 0.5062 which indicate that drug was released by non-fickian release mechanism.

Tablets were evaluated for physical parameters, *in-vitro* release profile and drug content, after one month and three months period there was no significant changes observed in any of the studied parameters during the study period. Stability study were carried out for Batch B8 by storing at 25°C/60%RH, 30°C/65%RH, 40°C/75%RH for three months. Thus, it could be concluded that formulation was stable.

Based on the observations and results, it was concluded that formulation B8 to be an ideal or optimized formulation for 12 hours release as it fulfills all the requirements for sustained release tablets. In future, *in-vivo* studies shall be carried out in correlation to the *in-vitro* release data for establishing the formulation as a product.

ACKNOWLEDGEMENTS

Authors are thankful to Dr. B. Jaykar, Prof. & Principal, Vinayaka Mission's College of Pharmacy, Salem, Tamil Nadu for extending their support and facilities for this research project.

REFERENCES

1. Lachman Leon, Liberman H.A. and Kanig J.L., "The Theory and Practice of Industrial pharmacy" 3rd edn, Varghese publishing House, Bombay, p. 430.
2. Brahmankar D. M. and Jaiswal S.B., in, "Biopharmaceutics and Pharmacokinetics", "A Treatise", 1st edn, 1995, Vallabh Prakashan, 347-371.
3. Lachman Leon, Liberman H.A. and Kanig J.L., "The Theory and Practice of Industrial pharmacy", 3rd edn, Varghese publishing House, Bombay, 346-372.
4. SurapaneniMS,DasSK and Das NG," The effect of excipients and processing variables on adhesive properties and release profile of pentoxifylline from mucoadhesive tablets",Idaho state university,Procatello,USA.
5. Palanisamy. P and B.Jaykar "Formulation and evaluation of controlled release mucoadhesive matrix tablet of nadolol", world journal of pharmaceutical research, 2015, Volume 4, Issue 8, 1223-1232.
6. R.Margret Chandira, P.Palanisamy, B.Jayakar "Design And Development Of Controlled Release Mucoadhesive Oral Tablet Of Clarithromycin", International Journal of Pharma Recent Research, 2009, 1(1), Page. No: 59-66
7. R.Margret Chandira, P.Palanisamy, B.Jayakar "Formulation and Evaluation of Effervescent Tablets of Aceclofenac", International Research Journal of Pharmacy, December--2011; Volume.no:2, Issue (12), Page. no: 185-190.
8. Palanisamy. P, Jaykar. B, Margret Chandira. R, B.S.Venkateswarlu, "Formulation and Charaterization of Pulsatile Drug Delivery System Containing Antiasthmatic Drug" IJDDT, Vol.3 No.1 January-June 2013, pp. 1-16.
9. Palanisamy. P, R. Margret Chandira, B. Jaykar, A.Pasupathi, B. S. Venkateshwarlu, M. Kumar, M. V. Kumudhavalli, "Formulation and evaluation of inlay tablet of metformin hydrochloride as sustained release and pioglitazone with glibenclamide as immediate release" , Journal of Pharmacy Research, 2014,8(11),Page. No: 1592-1607.
10. R.Margret Chandira, P.Palanisamy, B.Jayakar "Formulation and Evaluation of Isoniazid and Ethambutol Hydrochloride Combination Tablets", International Research Journal of Pharmacy (IRJP), February-2012; Volume.no:3, Issue (2), Page. no: (90-97).

11. R.Margret Chandira, P.Palanisamy, B.Jayakar "Formulation and Evaluation of Bilayered Floated Tablets of Metformin Hydrochloride", International Research Journal of Pharmacy (IRJP), February-2012; Volume.no:3, Issue (2), Page. no: (257-266).
12. LV Allen and PE Luner, Magnesium Stearate, in "Handbook of Pharmaceutical Excipients" IInd edition, edited by Arthur H. Kibbe, American Pharmaceutical Association, Washington D.C. Published by Pharmaceutical Press, London, UK, 305-308.
13. E Morefield, Colloidal Silicon dioxide, in "Handbook of Pharmaceutical Excipients" IInd edition, edited by Arthur H. Kibbe, American Pharmaceutical Association, Washington D.C. Published by Pharmaceutical Press, London, UK, 143-145.
14. Haung Y., Khanvilkar KH, Moore AD, Hilliard Lott M. in "Drug Development and Industrial Pharmacy", 2003, 29 (1) 79- 88.
15. Pandey VP, Manavalan R, Sunder Rajan T, Ganesh KS, in "Indian Journal of Pharmaceutical Science", 2003, 65 (1), 44-48.
16. Ahlneck, C., and Zografi. 1990. The molecular Basis of moisture effects on the physical and chemical stability of drugs in the solid state, Int. J. Pharm. 62: 87-85.
17. ICH Guideline Published by Europian Medicines agency CAMP /ICH/ 2736/99 August 2003.

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