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FORMULATION AND EVALUATION OF BOSENTAN PULSATILEDRUG DELIVERY SYSTEM BY USING PRESS COAT TECHNIQUE

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ABSTRACT

In the present research work, we have designed a pulsatile formulation of Bosentan to treat High blood pressure as per the chronotherapeutic pattern of the disease. Core tablets were prepared by incorporating different concentration of disintegrants and were compressed in between different concentration of polymers. The core and compression coated tablets were subjected to pre- formulation, physicochemical and *In-vitro* drug release studies. FTIR studies revealed that there was not any chemical reaction between pure drug Bosentan and polymers. The pre and post- compressional parameters of tablets were also found to be within limits. Our optimized formulation F-6 releases Bosentan after a lag time of 2 hours and 98.01 % up to 12 hours. Formulations were stable for at least 3 months under standard long-term and accelerated storage conditions.

KEYWORDS: Pulsatile formulation, Bosentan, Croscarmellose sodium, Carbopol 974P, HPMC K15, Ethyl cellulose and Compression coated tablets.

INTRODUCTION

Oral drug delivery is the largest segment of the total drug delivery market. It is the most preferred route for drug administration. The oral controlled-release systems show a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time, thereby ensuring sustained therapeutic action. There are certain conditions for which such a release pattern is not suitable that demand release of a drug after a lag time. In other words, they require pulsatile drug delivery system (PDDS). The pulsatile system is gaining a lot of interest, as the drug is released completely after defined lag time. Pulsatile drug delivery is time and site-specific drug delivery, thus providing spatial and temporal delivery and increasing patient compliance. Pulsatile drug delivery is defined as the rapid and transient release of certain amount of molecules within a short time period immediately after a predetermined off-released period, i.e., lag time, or these systems have a peculiar mechanism of delivering the drug rapidly and completely after a lag time, i.e., a period of no drug release. Such a release pattern is known as pulsatile release.[1-4]

Humans exhibit endogenous circadian rhythms that are regulated by the master circadian clock of the body, the suprachiasmatic nucleus. Chronopharmacotherapy of diseases (bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer and hypertension) (Table 1) that show circadian rhythms in their pathophysiology and treatment of such diseases require pulsatile drug delivery systems, by which drug is released rapidly and completely as a pulse after a lag time.[5-7] There are many other conditions that demand pulsatile release, like many body functions that follow circadian rhythms, such as secretion of hormones [including follicle stimulating hormone (FSH), luteinizing hormone (LH), luteinizing hormone releasing hormone (LHRH), estrogen and progesterone], acid secretion in the stomach, gastric emptying and gastrointestinal blood transfusion. Drugs that produce biological tolerance demand a system that will prevent their continuous presence at the biophase, as this tends to reduce their therapeutic effect. The lag time is essential for drugs that undergo degradation in gastric acidic medium (e.g., peptide drug) and irritate the gastric mucosa or induce nausea and vomiting. Targeting a drug to a distal organ of gastrointestinal tract (GIT), like the colon, requires that the release is prevented in the two-third portion of the GIT. Drugs (β-blockers or β-estradiol) that undergo first-pass metabolism, resulting in reduced bioavailability, altered steady-state levels of drug and metabolite and potential food drug interaction, require delayed released to the extent possible.[8-10] All the above attributes can be taken into account in designing a delivery system that exhibits pulsatile release characteristics and releases the drug in a predetermined fashion at a particular site.

The rationale of this study is to design and characterize an oral pulsatile drug delivery system containing Bosentan.

Bosentan, sold under the brand name Tracleer and Safebo among others, is a dual endothelin receptor antagonist medication used in the treatment of pulmonary artery hypertension.

The present study focuses on the development of pulsatile release tablets of Bosentan at a per oral, time - controlled single-unit dosage form. The proposed system consists of a core tablet coated with two layers, an inner swelling layer and an outer rupturable coating. The swelling layer is composed of super disintegrant and Micro crystalline cellulose (MCC) as a diluent, while the rupturable coating is Eudragit RSPO, Sodiumcarboxy methylcellulose and Carbopol p934.

MATERIALS AND METHODS

Materials

Bosentan Provided by SURA LABS, Dilsukhnagar. Croscarmellose sodium purchased from Yarrow Chem. Products, Mumbai. Carbopol 974P, HPMC K15, Ethyl cellulose purchased from SD Fine Chemicals, Mumbai. PVP K30 purchased from FMC Biopolymers.

Methodology

Analytical method development:

Preparation of calibration curve in 0.1N HCL:

10mg of Bosentan pure drug was dissolved in 10 ml of methanol (stock solution 1). 1ml of solution was taken and makes up with10 ml of 0.1N HCL (100µg/ml) stock-2. From this 1ml was taken and make up with 10 ml of 0.1N HCL (10µg/ml) stock-3. The above stock-II solution was subsequently diluted with 0.1N HCL to obtain series of dilutions containing and 2, 4, 6, 8 and 10µg/ml of solution. The absorbance of the above dilutions was measured at 270 nm for 0.1 N HCL by using UV-Spectrophotometer taking 0.1N HCL as blank. Then a graph was plotted bytaking 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 Same procedure repeated in pH 6.8 phosphate buffer.

Drug – Excipient compatibility studies fourier transform infrared (FTIR) spectroscopy

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany (Alpha T). The solid powder sample directly place on yellow crystal which was made up of ZnSe. The spectra were recorded over the wave number of 4000 cm^{-1} to 550 cm^{-1}.

Formulation development of tablets

Formulation of core tablets by direct compression: The inner core tablets were prepared by using direct compression method as shown in the Table 7.1. Powder mixtures of Bosentan, Croscarmellose sodium, Pvpk 30, Talc and Microcrystalline cellulose ingredients were dry blended for 20 min. followed by addition of Magnesium stearate. The mixtures were then further blended for 10 min., 200 mg of resultant powder blend was manually compressed using , Lab press Limited, India with a 7 mm punch and die to obtain the core tablet. Formulation of mixed blend for barrier layer: The various formulation compositions containing Carbopol 974P, HPMC K15, Ethyl cellulose, Talc and Microcrystalline Cellulose. Different compositions were weighed dry blended at about 10 min and used as press coating material to prepare press-coated pulsatile tablets respectively by direct compression method.

Preparation of press-coated tablets: The core tablets were press-coated with 100 mg of mixed blend as given in Table. No 7.2. 150 mg of barrier layer material was weighed and transferred into a 6mm die then the core tablet was placed manually at the center. The remaining of the barrier layer materiel was added into the die and compressed by using Lab press Limited, India.

Table 1: Formulation development of core tablets.

Ingredients	C1	C2	C3
Bosentan	62.5	62.5	62.5
Croscarmellosesodium	30	60	90
Pvpk 30	10	10	10
Magnesium stearate	3	3	3
Talc	2	2	2
Microcrystalline cellulose	Q.S	Q.S	Q.S
Total weight	200	200	200

Table 2: Formulations for press coated tablets.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Carbopol 974P	20	40	60	-	-	-	-	-	-
HPMC K15	-	-	-	20	40	60	-	-	-
Ethyl cellulose	-	-	-	-	-	-	20	40	60
PVP K30	15	15	15	15	15	15	15	15	15

Magnesium Stearate	3	3	3	3	3	3	3	3	3
Microcrystalline cellulose	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Talc	2	2	2	2	2	2	2	2	2
Total weight	100	100	100	100	100	100	100	100	100

RESULTS AND DISCUSSION

Presentstudywasdoneonpulsatiletabletswithdifferentformulations F1toF9.Formulations had weight ratio of polymers like Carbopol 974P, HPMC K15, and Ethyl cellulose along with various excipients.

Preformulation studies

Standardization method for estimation of bosentan

Standard curves of Bosentan were prepared in 0.1NHCL and phosphate buffer (pH 6.8). Standard graph of Bosentanin 0.1N HCL: Bosentan showed maximum absorbance in 0.1NHCL at 270nm.The solution obeyed Beer Lambert' slaw for concentration range of 0µg/mLto10µg/mL with regression coefficient of 0.997.Standard curve of Bosentan preparedin 0.1NHC Lis shown below inTable 3 and Figure5.1.

Table 3: Calibration data of Bosentan 0.1NHCL.

Concentration [µg/ml]	Absorbance
0	0
2	0.132
4	0.249
6	0.354
8	0.478
10	0.571

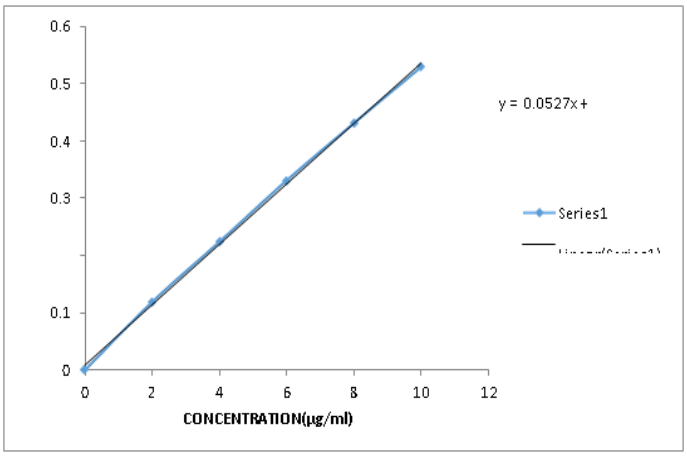

Fig. 1: Standard Graph of Bosentanin 0.1NHCL.

Standard graph of Bosentan in phosphate buffer (pH6.8) Bosentan showed maximum absorbance in phosphate buffer (pH 6.8) at 274 nm. The solution obeyed Beer-Lambert's law for concentration range of 0 to 10 µg/mL with regression coefficient of 0.999. Standard curve of prepared Bosentan in phosphate buffer pH 6.8isshownbelow.

Table 4: Calibration data of Bosentan in pH6.8 phosphate buffer.

Conc[µg/ml]	Abs
0	0
2	0.119
4	0.224
6	0.331
8	0.431
10	0.529

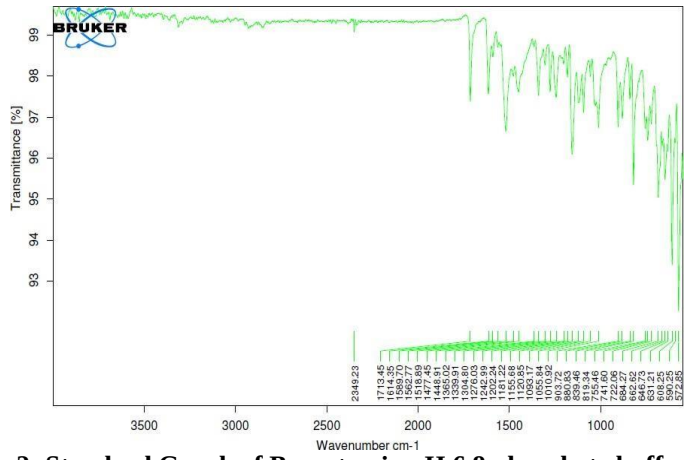

Fig. 2: Standard Graph of Bosentan in pH 6.8 phosphate buffer5.3.

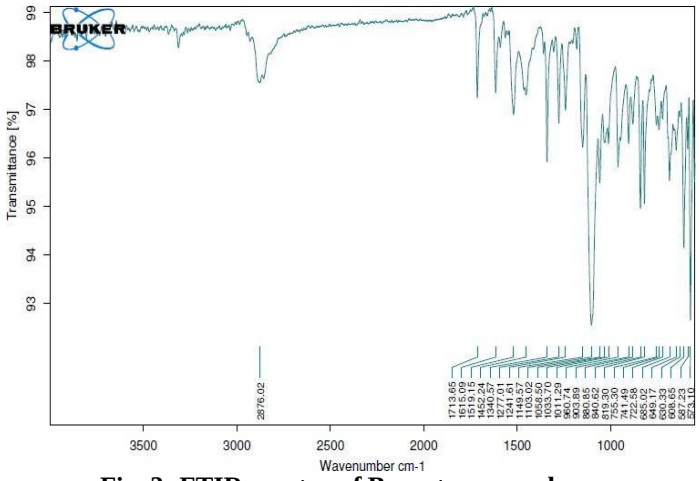

Fig. 3: FTIR spectra of Bosentan pure drug.

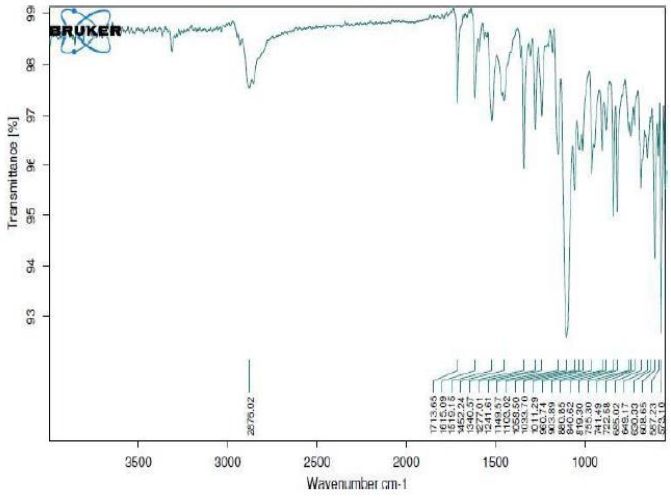

Fig. 4: FTIR spectra of optimized formula.

The spectra for pure Bosentan and for the physical mixture of Bosentan and all thepolymers were determined to check the intactness of the drug in the polymer mixture using FTIR Spectrophotometer.

The comparative FTIR studies of Drug and excipients combination had shown negligible variation in the values as compared with that of only pure form of Drug. Therefore, it implies good compatibility of drug and excipients.

From the above table, the wave number of mixture of drug with excipients is within the range of wave number of pure drug.

Table 5: Precompression parameters of Cap core tablets.

Formulation Code	Angle ofrepose (o)*	Bulkdensity (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
C1	21.75±0.04	0.52±0.14	0.617±0.09	14.45±0.72	1.1655±0.05
C2	21.83±0.03	0.54±0.13	0.628±0.08	14.89±0.55	1.1749±0.03
C3	20.95±0.01	0.53±0.01	0.618±0.01	14.43±0.41	1.1687±0.01

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 0.54± 0.13 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the rangeof0.617±0.09to0.628±0.08showingthepowderhasgoodflowproperties.Thecompressibility index of all the formulations was found to be ranging from 14.43± 0.41 to14.89±0.55 which were showed that the powder has good flow properties. All the formulations has shown the hausner ratio ranging from 1.1655± 0.05 to 1.1749± 0.03 indicating the powder has good flow properties.

Table 6: Post compression parameters of core tablet.

Formulation code	Average Weight (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drugc ontent (%)	*Invitro* disintegration time (min)
C1	199.95	4.6	0.36	3.98	99.31	35
C2	200.26	4.2	0.25	3.82	98.14	26
C3	199.14	4.3	0.23	3.90	100.09	20

The *in vitro* disintegration time values for all the formulations were found to be in the range of 20 to35.

Table 7: Pre compression parameters of bosentan coated tablets.

Formulation code	Angle of repose(o)*	Bulk density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner's Ratio
F1	22.59±0.33	0.432±0.14	0.506±0.01	17.54±0.17	1.298±0.44
F2	24.19±0.16	0.511±0.03	0.614±0.11	22.27±0.05	1.276±0.12
F3	26.21±0.19	0.481±0.05	0.517±0.06	18.92±0.14	1.313±0.16
F4	23.53±0.05	0.513±0.12	0.498±0.19	19.21±0.11	1.299±0.04
F5	24.77±0.18	0.402±0.09	0.477±0.23	20.04±0.03	1.303±0.08
F6	27.23±0.17	0.326±0.98	0.596±0.02	17.04±0.06	1.276±0.16
F7	25.99±0.15	0.491±0.29S	0.542±0.17	18.99±0.09	1.206±0.12
F8	26.54±0.09	0.394±0.16	0.603±0.04	21.15±0.15	1.193±0.99
F9	22.05±0.03	0.451±0.07	0.481±0.18	19.93±0.26	1.266±0.17

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 0.326±0.98– 0.511±0.03 (gm/cm^3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.477±0.23, 0.614±0.11 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging from 17.04±0.06 to22.27±0.05 which show that the powder has good flow properties. All the formulations have shown the hausner ratio ranging between 1.193±0.99 to 1.313±0.16 indicating the powder has good flow properties.

Table 8: Post compression parameters of coated tablet.

Formulation code	Average Weight(mg)	Hardness (kg/cm2)	Thickness	Friability (%loss)	Drug content (%)
F1	99.39	5.3	3.69	0.36	98.30
F2	98.72	5.6	3.58	0.58	99.12
F3	100.01	5.9	3.31	0.42	98.25
F4	98.25	5.0	3.92	0.30	97.10
F5	97.66	5.6	3.76	0.18	96.32
F6	96.85	5.3	3.86	0.27	98.53
F7	98.50	5.1	3.51	0.62	99.14
F8	98.21	5.8	3.93	0.51	98.99
F9	99.15	5.4	3.75	0.73	98.35

***In vitro* drug release studies of bosentan core tablet:**
In vitro dissolution studies of Bosentan core tablets were performed using USP XXIII Type II rotating paddle dissolution apparatus by using phosphate buffer (pH 6.8) as a dissolution medium. From formulation C1-C3 Bosentan core tablets, C3 showed faster drug release than the other formulations. Faster drug release can be correlated with the high disintegration time. So,C3 formulation was selected as best formulation for further press coating and enteric coating formulations. *In vitro* drug release profiles of all Bosentan core tablets were shown in Table.

Table 9: Drug release of bosentan core tablets.

Time(min)	C1	C2	C3
0	0	0	0
5	25.19	32.21	43.36
10	40.57	45.26	56.81
15	47.36	58.62	69.06
20	53.19	67.73	77.43
30	65.98	78.89	82.99
45	72.52	85.11	92.35
60	83.42	92.34	99.73

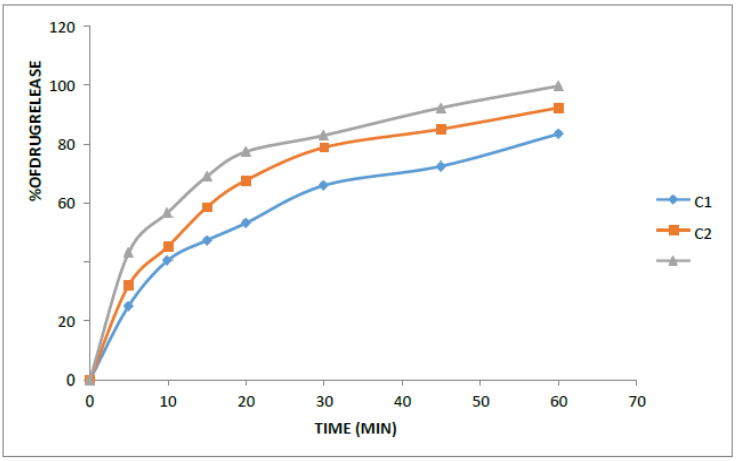

Fig. 5: Cumulative % drug released of Bosentan core tablets.

***Invitro* drug release study of bosentan pulsatile tablets**
Based on the above characters formulation C3 was selected as best formulation and thatC3 formulation were used for the further study.

Table 10: Cumulative % drug release of coated bosentan tablets containing carbopol974p.

Time (hr)	F1	F2	F3
0	0	0	0
0.5	0.51	0.30	0.21
1	4.49	1.81	0.92
2	5.14	4.96	2.81
3	40.36	37.93	32.72
4	45.91	40.65	38.40
5	51.52	46.49	44.11
6	68.40	55.66	50.82
7	73.98	65.91	63.97
8	87.12	72.54	66.34
9	96.76	73.28	71.77
10		85.41	84.82
11		92.09	90.91
12			96.89

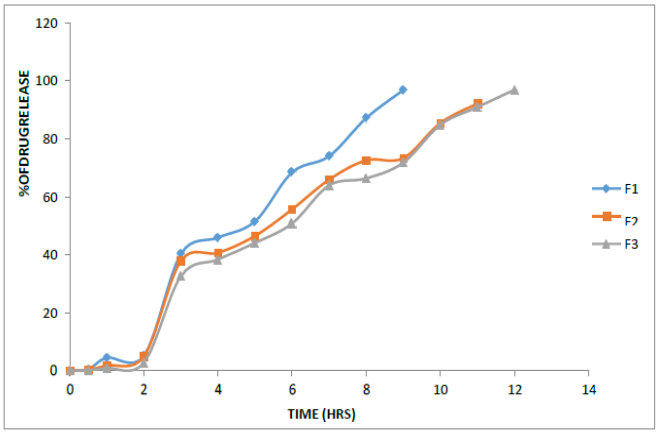

Fig. 6: Cumulative % drug release study of Bosentan pulsatile tablets (F1, F2&F3).

The formulations F1 to F3 were containing Carbopol 974P. At low concentration such as 15 mg of Carbopol 974P was able to delay the drug release.

Table 11: Cumulative% drug release of Coated Bosentan tablets containing HPMCK15.

Time (hr)	F4	F5	F6
0	0	0	0
0.5	1.39	0.52	0.14
1	2.52	1.14	1.01
2	4.81	3.76	2.43
3	43.26	35.83	28.79
4	56.81	47.91	34.67
5	69.99	53.25	41.33
6	78.53	67.56	52.10
7	83.19	75.90	60.79
8	91.46	81.11	75.21
9	98.82	85.47	80.34
10		90.59	86.13
11		93.76	95.59
12		96.93	98.06

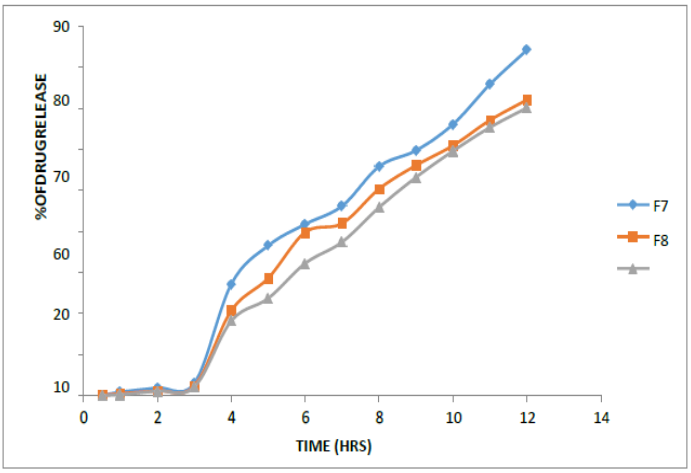

Fig. 7: Cumulative % drug release study of Bosentan pulsatile tablets (F4, F5& F6).

Table 12: Cumulative % drug release of coated Bosentan tablets containing Ethyl cellulose.

Time (hr)	F7	F8	F9
0	0	0	0
0.5	0.82	0.50	0.23
1	1.86	1.16	1.10

2	2.92	2.29	2.02
3	27.17	20.71	18.21
4	36.53	28.63	23.69
5	41.75	39.82	32.23
6	46.19	41.95	37.42
7	55.83	50.38	45.87
8	59.71	56.12	53.21
9	66.11	60.95	59.62
10	75.86	67.12	65.37
11	84.25	72.10	70.15
12	93.93	89.57	87.21

The formulations F7 to F9 were containing Ethyl cellulose. At low concentration such as40, 60 mg of Ethyl cellulose was unable to delay the drug release up to desired time hence that formulations were not considered. Then the coating polymer concentration was increased to60mg F 9 was showedmaximum% drugrelease87.21%at12hours.

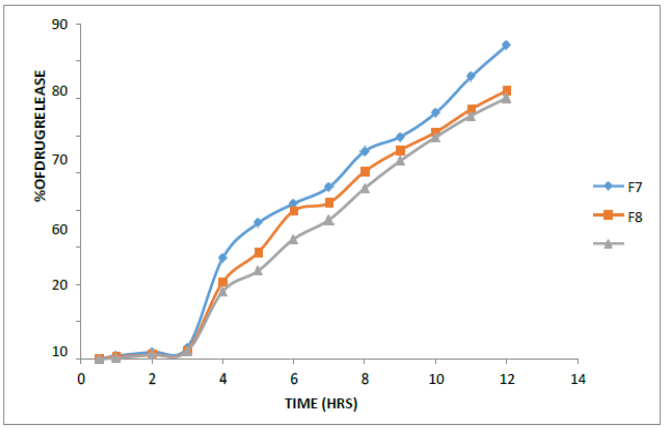

Fig. 8: Cumulative % drug release study of Bosentan pulsatile tablets (F7, F8, F9).

Release kinetics

Data of *in vitro* release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of Bosentan release from buccal tablets. The data was fitted into various kinetic models such as zero, first order kinetics; Higuchi and korseyer peppas mechanisms and the results were shown in below table.

Table 13: Release Kinetics and Correlation coefficients (R2).

Cumulative (%) releaseq	Time (T)	Root (T)	Log (%) relea se	Log (T)	Log (%) remai N	Releasera te (Cumulati ve %release/t)	1/CUM% release	Peppas log/ 100	%Drug Rema ining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
0.14	0.5	0.707	-0.854	-0.301	1.999	0.280	7.1429	-2.854	99.86	4.642	4.639	0.002
1.01	1	1.000	0.004	0.000	1.996	1.010	0.9901	-1.996	98.99	4.642	4.626	0.016
2.43	2	1.414	0.386	0.301	1.989	1.215	0.4115	-1.614	97.57	4.642	4.604	0.038
28.79	3	1.732	1.459	0.477	1.853	9.597	0.0347	-0.541	71.21	4.642	4.145	0.497
34.67	4	2.000	1.540	0.602	1.815	8.668	0.0288	-0.460	65.33	4.642	4.028	0.614
41.33	5	2.236	1.616	0.699	1.768	8.266	0.0242	-0.384	58.67	4.642	3.886	0.756
52.1	6	2.449	1.717	0.778	1.680	8.683	0.0192	-0.283	47.9	4.642	3.632	1.010
60.79	7	2.646	1.784	0.845	1.593	8.684	0.0165	-0.216	39.21	4.642	3.397	1.244
75.21	8	2.828	1.876	0.903	1.394	9.401	0.0133	-0.124	24.79	4.642	2.916	1.726
80.34	9	3.000	1.905	0.954	1.294	8.927	0.0124	-0.095	19.66	4.642	2.699	1.943
86.13	10	3.162	1.935	1.000	1.142	8.613	0.0116	-0.065	13.87	4.642	2.403	2.239
95.59	11	3.317	1.980	1.041	0.644	8.690	0.0105	-0.020	4.41	4.642	1.640	3.002
98.06	12	3.464	1.991	1.079	0.288	8.172	0.0102	-0.009	1.94	4.642	1.247	3.394

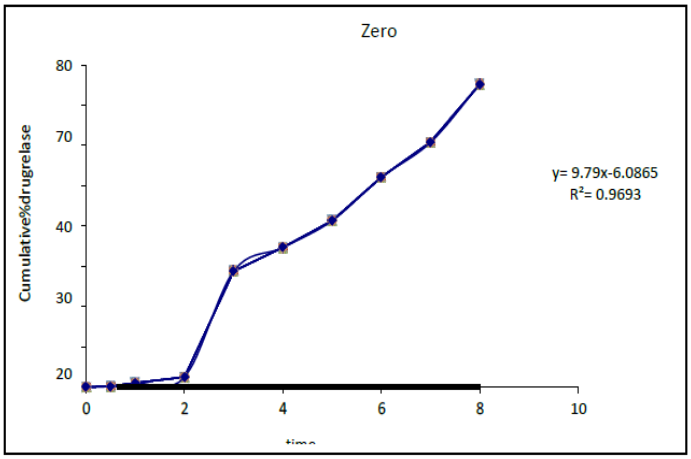

Fig. 9: Zero order plot of optimized formulation.

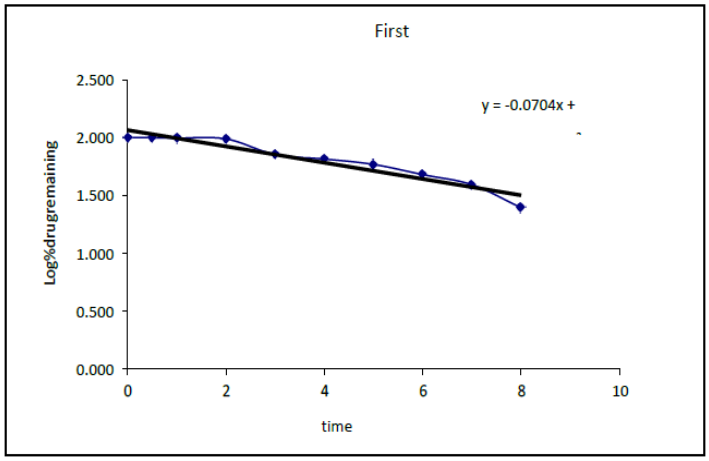

Fig. 10: First order plot of optimized formulation.

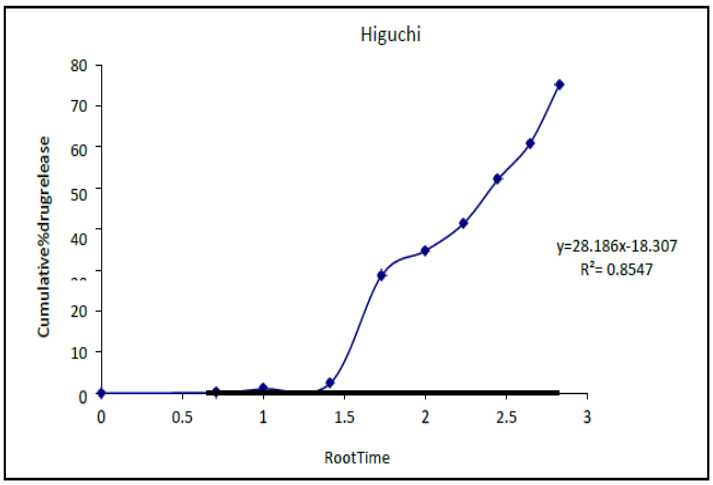

Fig. 11: Higuchiplot of optimized formulation.

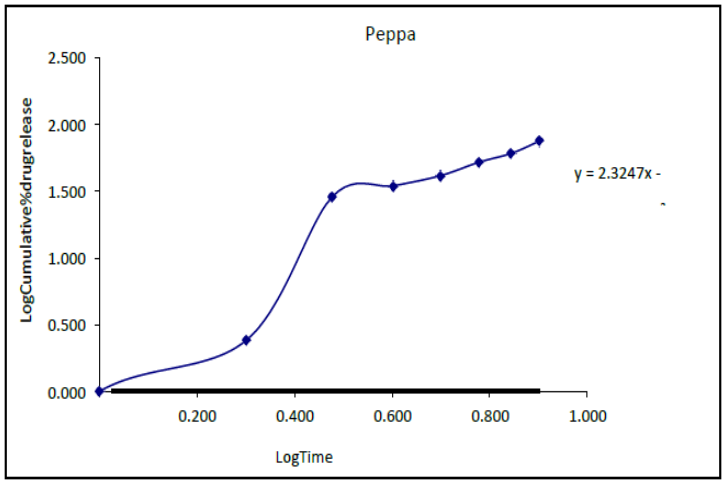

Fig. 12: Koresmeyer-peppas plot of optimized formulation.

This formulation was following Zero order release mechanism with regression value of 0.969.

Table 14: Stability studies of optimized formulation.

Time points	Initial	%OFDRUG RELEASE								
		25°C/60%RH			30°C/65%RH			40°C/75%RH		
		1st Month	2nd Month	3rd Month	1st Month	2nd Month	3rd Month	1st Month	2nd Month	3rd Month
0	0	0	0	0	0	0	0	0	0	0
0.5	0.14	0.13	0.13	0.11	0.12	0.11	0.10	0.16	0.14	0.14
1	1.01	1.05	1.03	1.03	1.00	0.65	0.56	1.03	1.00	1.01
2	2.43	2.40	2.35	2.25	2.41	2.12	2.10	2.32	2.25	2.10
3	28.79	28.71	28.68	28.51	28.21	27.53	27.41	28.25	27.81	27.51
4	34.67	34.62	34.52	34.49	34.51	34.12	33.82	34.16	34.12	33.89
5	41.33	41.28	41.26	41.20	41.22	41.02	41.05	41.03	40.67	40.51
6	52.1	52.02	52.00	51.98	52.01	52.00	51.91	51.56	51.43	51.26
7	60.79	60.51	60.42	60.26	60.43	60.26	60.23	60.11	60.02	59.93
8	75.21	75.13	75.10	75.02	75.11	75.01	74.91	75.09	74.86	74.62
9	80.34	80.26	80.23	80.15	80.25	80.3	79.89	80.24	80.12	80.04
10	86.13	86.10	86.08	86.01	86.03	85.89	85.62	86.00	85.89	85.71
11	95.59	95.46	95.32	95.26	95.43	95.31	94.82	95.19	95.76	95.20
12	98.06	98.05	98.03	98.02	98.03	98.01	98.01	98.04	98.02	98.01

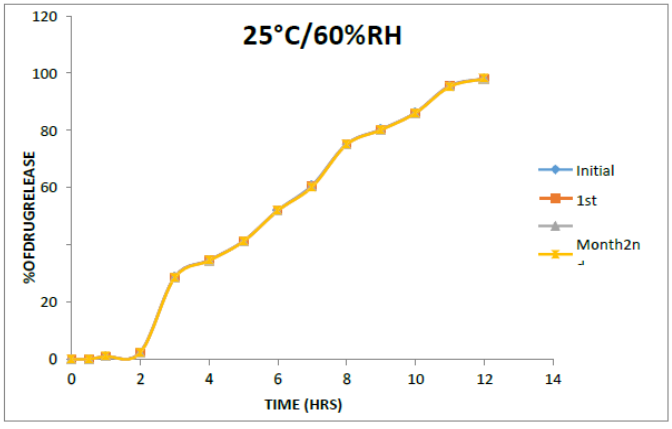

Fig. 13: Drug release profile of formulation F6 during stability.

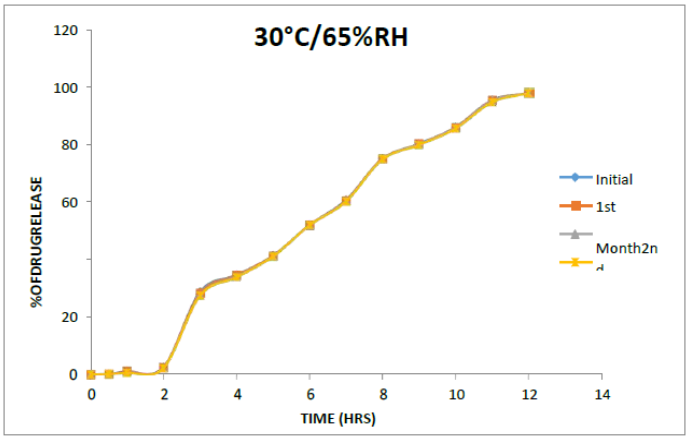

Fig. 14: Drug release profile of formulation F6 during stability.

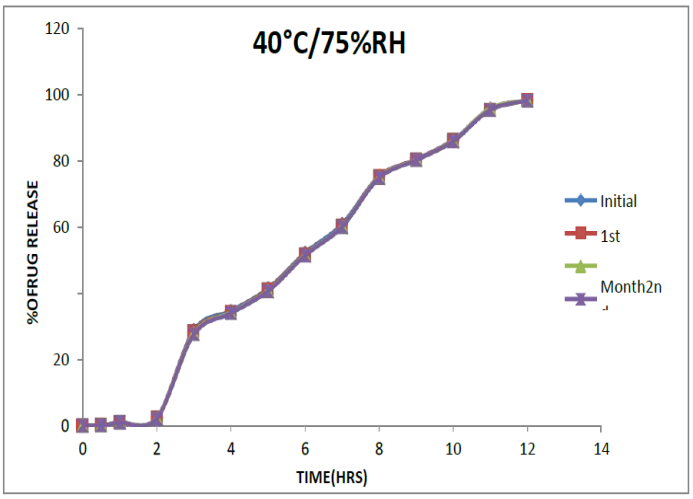

Fig. 15: Drug release profile of formulation F6 during stability.

Stability Studies were carried out at 25°C/60%RH, 30°C/65%RH and 40°C/75%RH for 90days.The core tablet and coated tablet of selected formulation were packed in amber-colored bottles tightly plugged with cotton and capped.

Table 15: Physico chemical parameters of most satisfactory formulation during stability studies for optimized formulation.

Time Period (M onth)	25°C/60%RH		30°C/65%RH		40°C/75%RH	
	Hardness	Drug Content	Hardness	Drug Content	Hardness	Drug Content
Initial	5.3	98.53	5.3	98.53	5.3	98.53
1	5.3	98.41	5.2	98.21	5.3	98.10
2	5.2	97.98	5.2	98.10	5.2	98.03
3	5.2	97.72	5.2	97.97	5.1	97.93

SUMMARY AND CONCLUSION

- ✓ A chronomodulated drug delivery system for Bosentan for the treatment of pulmonary artery hypertension was successfully developed. The system was found to be satisfactory in terms of release of the drug after a lag time of 2 hrs.
- ✓ The formulation (F6) HPMC K15 (60mg)) gave satisfactory release lag time of 2 hrs and it was found to be successful in achieving pulsatile drug delivery.
- ✓ The technology (press-coating) used for the preparation of press-coated pulsatile tablets (PCPT) is a relatively simple manufacturing process which can be easily adopted in industrial units on a commercial scale.
- ✓ From formulation C1-C3 Bosentan core tablets, C3 showed faster drug release than the other formulations. Faster drug release can be correlated with the high disintegration time. So, C3 formulation was selected as best formulation for further press coating and enteric coating formulations. Among All Formulations F6 was showed maximum % drug release 98.01 % at 12 hours. Hence F6 Formulation was considered as

optimized Formulation.

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