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Original Article

FORMULATION DEVELOPMENT AND *IN VITRO* EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF BOSENTAN BY USING SYNTHETIC POLYMERS

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ABSTRACT

Objective: Bosentan is an endothelin receptor antagonist (ERA) indicated for the treatment of Pulmonary arterial hypertension (PAH). The aim of the present study involves the development of sustained release matrix tablets of bosentan in order to release the drug in sustained and predictable manner.

Methods: Bosentan SR Matrix tablets were prepared by Wet granulation method. The tablets were evaluated for Hardness, Thickness, Friability and Drug content and were subjected to a 12 hours in vitro drug release studies.

Results: The amount of Bosentan released from the tablet formulations at different time intervals was estimated using a UV Spectroscopy method. Among all the formulations are prepared by using different polymers like HPMC K 4 M, HPMC K15 M at different ratios.

Conclusion: We Can Conclude that Among the Ten formulations, F-2 formulation containing drug to HPMC K 4 M in ratio 1:0.5 is optimized based on its ability to sustain drug release till 12 hours of dissolution study, The results of the study clearly demonstrated that HPMC matrix tablet formulation is an effective and promising drug delivery system for once daily administration of Bosentan.

Keywords: Bosentan monohydrate, Wet granulation method, Sustained Release Matrix, Hydroxy Propyl methyl Cellulose (HPMC).

INTRODUCTION

The oral route of administration has been used the most for both conventional and novel drug delivery systems. There are many obvious reasons for this, not the least of which would include acceptance by the patient and ease of administration. The types of sustained and controlled release systems employed for oral administration include virtually every currently known theoretical mechanism for such application. This is because there is more flexibility in dosage design, since constraints, such as sterility and potential damage at the site of administration, are minimized [1].

Sustained release dosage forms may be defined as any drug or dosage form modification that prolonged but not necessarily uniform release of drug. The goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period. This is usually accomplished by attempting to obtain zero-order release from the dosage form. Zero-order release constitutes the drug release from the dosage form that is independent of the amount of drug in the delivery system (i. e., constant release rate). Sustained release systems generally do not attain this type of release and usually try to mimic zero-order release by providing drug in a slow first-order fashion (i. e., concentration dependent). Systems that are designated as prolonged release can also be considered as attempts at achieving sustained release delivery [1, 3].

Over the past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, the goal in the designing sustained –or controlled delivery system is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery [2].

Bosentan is a endothelin receptor antagonist used in the treatment of pulmonary artery hypertension (PAH). It is readily absorbed from the gastrointestinal tract with oral bioavailability of about 50% and a plasma elimination half-life is 5 hours. Administration of Bosentan in a sustained release dosage form would be more desirable by maintaining the plasma concentrations of the drug well above the therapeutic concentration.

MATERIALS AND METHODS

Materials

Bosentan was provided by MSN Laboratories Pvt. Ltd, Hyderabad, HPMC grades were procured from Yarrow Chem. Products, Mumbai, PVP- K 30, Talc, Magnesium stearate, and MCC was bought from Signet Chem., Mumbai.

Methodology

Preformulation Studies

Standardization of Bosentan by UV-Visible Spectrophotometry in 0.1 N Hcl Solutions

Preparation of stock solution

Stock solution 100µg/ml of Bosentan was prepared in 0.1N Hcl solution. This solution was approximately diluted with 0.1N Hcl to obtain a concentration of 10µg/ml. The resultant solution was scanned in the range of 200- 400 nm using UV double beam spectrophotometer (Lab India UV-3000+).

Standard calibration of Bosentan in 0.1N Hcl

100mg of Bosentan was accurately weighed and dissolved in100 ml of 0.1N Hcl to obtain a concentration of 1000µg/ml. From the above 10 ml was withdrawn and diluted to 100 ml to obtain a concentration of 100µg/ml. From this stock solution aliquots of 0.5 ml, 1 ml, 1.5 ml, 2 ml and 2.5 ml were diluted in 10 ml volumetric flask with phosphate buffer to give concentrations in range of 10µg/ml to 70µg/ml respectively, absorbance was measured at 242 nm.

Standardization of Bosentan by UV-Visible Spectrophotometry in p^H 6.8 Solutions

Preparation of stock solution

Stock solution 100µg/ml of Bosentan was prepared in phosphate buffer of pH 6.8. This solution was approximately diluted with

phosphate buffer of pH 6.8 to obtain a concentration of 10µg/ml. The resultant solution was scanned in range of 200- 400 nm using UV double beam spectrophotometer (Lab India UV-3000+).

Standard calibration of Bosentan in phosphate buffer of pᴴ 6.8

100mg of Bosentan was accurately weighed and dissolved in 100 ml of pH 6.8 phosphate buffer to obtain a concentration of 1000µg/ml. From the above 10 ml was withdrawn and diluted to 100 ml to obtain a concentration of 100µg/ml.

From this stock solution aliquots of 0.5 ml, 1 ml, 1.5 ml, 2 ml and 2.5 ml were diluted in 10 ml volumetric flask with phosphate buffer to give concentrations in range of 5µg/ml to 20µg/ml respectively, absorbance was measured at 243 nm.

Drug- Excipient Compatibility by FTIR studies

In the preparation of Sustained release tablet, drug and polymer may interact as they are in close contact with each other, which could lead to instability of the drug. Preformulation studies regarding drug-polymer interactions are therefore very critical in selecting appropriate polymers.

FT-IR spectroscopy (Agilent) was employed to ascertain the compatibility between bosentan and selected polymers. The individual drug and drug with excipients were scanned separately.

Procedure

Potassium bromide was mixed with drug and polymer in the ratio of 100:1 and pellet was prepared using KBr pellet press and spectrum was taken using FTIR (Agilent). FT-IR spectrum of bosentan was compared with spectrum of bosentan and polymer. Disappearance of bosentan peaks or shifting of peak in any of the spectra was studied.

Angle of repose

The angle of repose of blends was determined by the funnel method. The accurately weighed blend was taken in funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the blend. The blend was allowed to flow from the funnel on the surface. The diameter and height of the heap formed from the blend were measured. The angle of repose was calculated using following formula [3].

Tan Θ= h/r

Where, "h" is height of the heap and "r" is the radius of the heap of granules.

Carr's compressibility index

The Carr's compressibility Index was calculated from Bulk density and tapped density of the blend. A quantity of 2g of blend from each formulation, filled into a 10 mL of measuring cylinder. Initial bulk volume was measured, and cylinder was allowed to tap from the height of 2.5 cm. The tapped frequency was 25±2 per min to measure the tapped volume of the blend. The bulk density and tapped density were calculated by using the bulk volume and tapped volume. Carr's compressibility index was calculated by using following formula.

Carr's compressibility index (%) = [(Tapped density-Bulk density) X100]/Tapped density

Bulk Density (BD)

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced in to a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume. The bulk densities (BD) of powder blends were determined using the following formula.

Bulk density = Total weight of powder / Total volume of powder

Tapped bulk density (TBD)

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The tapped bulk densities (TBD) of powder blends were determined using the following formula. [4].

TBD= Total weight of powder / Total volume of tapped powder

Preparation of tablets

Wet granulation method

All the powders were passed through 80 mesh. Required quantities of all ingredients were mixed thoroughly and a sufficient volume of granulating agent was added slowly. After enough cohesiveness was obtained, the mass was sieved through 22/44 mesh. The granules were dried at 40 C for 12 hrs. Once, dry the granules retained on 44 mesh were mixed with 10% of fine granules that passed through 44 mesh. Talc and magnesium stearate were added as glidant and lubricant. In all formulations, the amount of the active ingredient is equivalent to 62.5 mg of Bosentan (Table 1).

Table 1: Formulations Containing HPMC K 4 M, HPMC K 15 M (Wet granulation)

S. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Bosentan	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5
2	HPMC K 4 M	15.62	31.25	62.5	93.75	125	---	---	---	---	---
3	HPMC K 15 M	---	---	---	---	---	15.62	31.25	62.5	93.75	125
4	PVP-K 30 (5%)	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS
5	Talc	6	6	6	6	6	6	6	6	6	6
6	Mg. Stearate	6	6	6	6	6	6	6	6	6	6
7	MCC	209.8	194.25	163	131.75	100.5	209.8	194.25	163	131.75	100.5
	Total Weight	300	300	300	300	300	300	300	300	300	300

Evaluation of tablets

The weight of tablets was evaluated on 20 tablets using an electronic balance. Friability was determined using 6 tablets in Roche friability tester at 25rpm. Hardness of the tablets was evaluated using a Monsanto hardness tester. The hardness of all the formulation was between 4-5 kg/cm^2.

***In vitro* dissolution studies**

In vitro drug release studies from the prepared matrix tablets were conducted using USP type II apparatus at 37^{0}C ±0.5^{0}C at 50rpm. Dissolution mediums used were 900 mL of 0.1N HCl and phosphate buffer of pH 6.8. The release rates from SR matrix tablets were conducted in HCl solution (pH 1.2) for 2 hrs and changed to phosphate buffer (pH 6.8) for further time periods. The samples were withdrawn at desired time periods from dissolution media and the same were replaced with fresh dissolution media of respective pH. The samples were analyzed by UV-Visible Spectrophotometer (Lab India 3000+). The amounts of drug present in the samples were calculated with the help of appropriate calibration curves constructed from reference standards. Drug dissolved at specified time periods was plotted as percent release versus time curve [5,6].

Dependent-model method (Data analysis)

In order to describe the Bosentan release kinetics from individual tablet formulations, the corresponding dissolution data were fitted in various kinetic dissolution models: zero order, first order,

Higuchi, Korsmeyer Peppas. When these models are used and analyzed in the preparation, the rate constant obtained from these models is an apparent rate constant. The release of drugs from the matrix tablets can be analysed by release kinetic theories. To study the kinetics of drug release from matrix system, the release data were fitted into Zero order as the cumulative amount of drug release vs. time (Eqn.3), first order as log cumulative percentage of drug remaining vs. time (Eqn.4), Higuchi model as cumulative percent drug release vs. square root of time (Eqn.5). To describe the release behavior from the polymeric systems, data were fitted according to well known exponential Korsmeyer – Peppas equation as log cumulative percent drug release vs log of time equation (Eqn.6).

(i) Zero order kinetics

Qt=K0t……Eqn.(3)

Where,

Q= Amount of drug release in time t

K0 = Zero order rate constant expressed in unit of concentration /time, t = Release time

(ii) First order kinetics

Log Q=Log Q0-kt/2.303……Eqn.(4)

Where, Q0= is the initial concentration of drug

k= is the first order rate constant

t =release time

(iii) Higuchi kinetics

Q=kt1/2……Eqn.(5)

Where, k= Release rate constant

t=release time, Hence the release rate is proportional to the reciprocal of the square root of time.

(iv) Korsmeyer-Peppas

First 60% *in vitro* release data were fitted in an equation of Korsmeyer et al. to determine the release behavior from controlled release polymer matrix system. The equation is also called as power law,

Mt /M∞ =Kt n …… Eqn.(6)

Where,

Mt = amount of drug released at time t

M∞ = amount of drug released after infinite time

Mt /M∞ = fraction solute release

t = release time

K = kinetic constant incorporating structural and geometric characteristics of the polymer system

n = diffusional exponent that characterizes the mechanism of the release of traces. The magnitude of the release exponent "n" indicates the release mechanism (i. e. Fickian diffusion, Non Fickian, supercase II release).

For matrix tablets, values of n of near 0.5 indicates Fickian diffusion controlled drug release, and an n value of near 1.0 indicates erosion or relaxational control (case II relaxational release transport, non Fickian, zero order release). Values of n between 0.5 and 1 regarded as an indicator of both diffusion and erosion as overall release mechanism commonly called as anomalous release mechanism [7].

RESULTS AND DISCUSSION

Preformulation characteristics

The drug Bosentan was standardized by UV method in 0.1N Hcl and pH 6.8 Buffer separately. The lambda max were 242 nm and 243 nm in 0.1N Hcl and pH 6.8 buffer respectively and the linearity range was 5-70 mcg/ml in both the media.

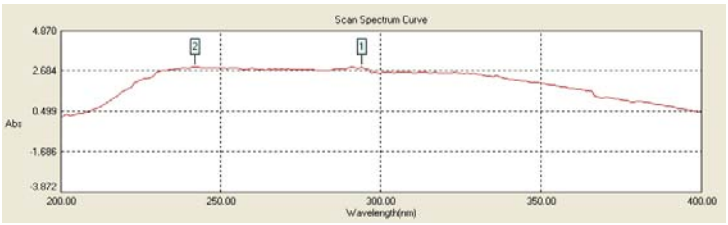


Fig. 1: λ_{max} of Bosentan in 0.1 N HCl (242 nm)

Table 2: Absorbences of Bosentan in 0.1N HCL

S. No.	Concentration(mcg/ml)	Absorbance(nm)
1	10	0.141
2	20	0.207
3	30	0.293
4	40	0.390
5	50	0.470
6	60	0.547
7	70	0.654

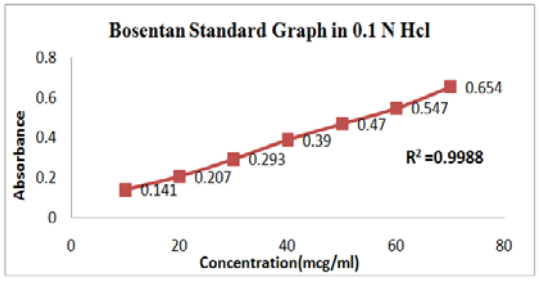


Fig. 2: Calibration curve of Bosentan in 0.1N HCL

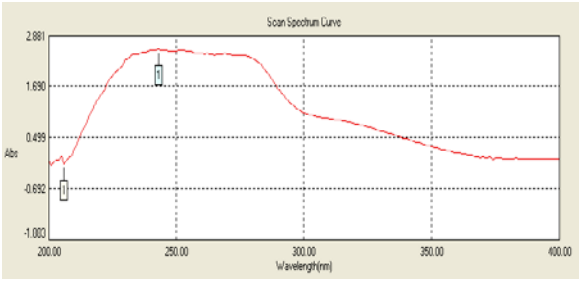


Fig. 3: λ_{max} of Bosentan in pH 6.8 Buffer (243 nm)

Table 3: Absorbences of Bosentan in 6.8 pH Phosphate buffer

S. No.	Concentration(mcg/ml)	Absorbance (nm)
1	5	0.356
2	10	0.585
3	12	0.683
4	15	0.821
5	18	0.997
6	20	1.081

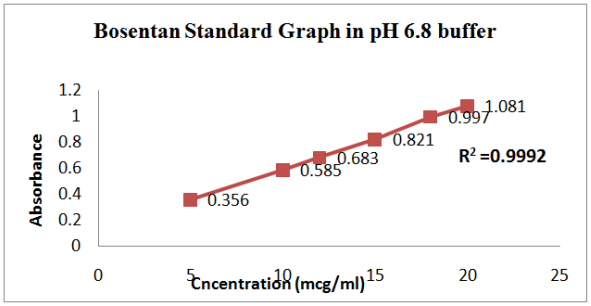


Fig. 4: Calibration curve of Bosentan in 6.8 pH Phosphate buffer

Drug Excipient Compatibility Studies- FTIR

Drug-Excipient compatibility studies by FTIR revealed no interaction between drug and the polymers used in the formulation thus showing compatibility.

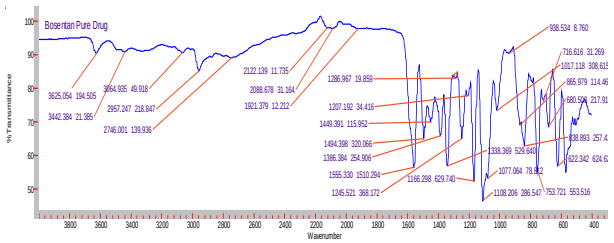


Fig. 5: FTIR spectra of Bosentan pure Drug

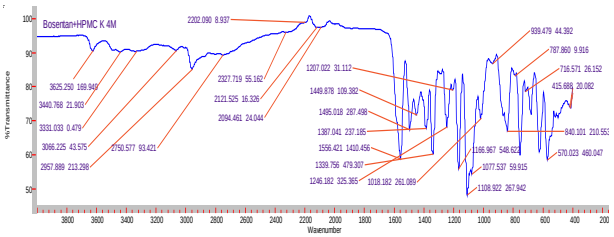


Fig. 6: FTIR spectra of Bosentan pure Drug + HPMC K 4 M

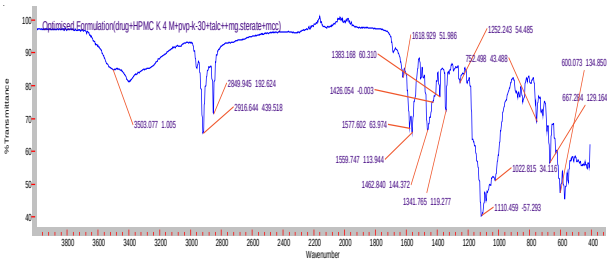


Fig. 7: FTIR spectra of Optimized Formulation (Bosentan+HPMC K 4 M+PVP-K 30+Talc+Mg. Stearate+MCC)

Differential Scanning Calorimetry (DSC):

The compatibility and interactions between drugs and polymer were checked using differential scanning calorimetry (DSC). Any possible drug polymer interaction can be studied by thermal analysis.

The DSC study was performed on pure drug (Bosentan) and Optimized Formulations (drug + HPMC K4M + pvp k 30 + talc + Mg. Stearate + Mcc). The study was carried out using Hitachi 6300.

The 2 mg of sample were heated in a hermetically sealed aluminum pans in the temperature range of 30-220°c at heating rate of 10°c /min under nitrogen flow of 40 ml/min. Finally hence their no interaction was found between drug and the polymers.

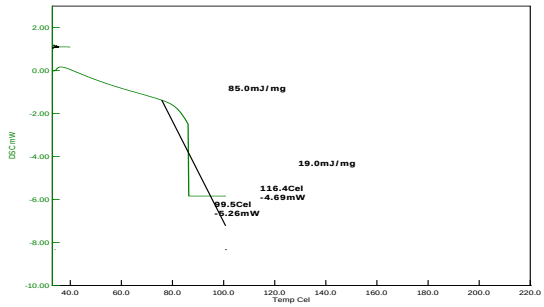


Fig.8: Differential Scanning Calorimetry analysis of Bosentan Pure Drug.

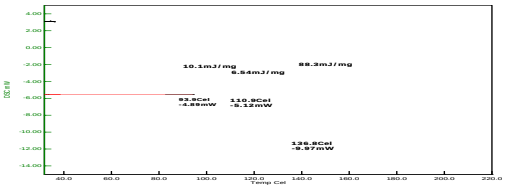


Fig. 9: Differential Scanning Calorimetry analysis of Optimized Formulation (Drug+HPMCK4M+PVP k 30+Talc+Mg. Stearate+Mcc)

Physical characteristics of blends and tablets

The blends of different formulations were evaluated for angle of repose, Carr's compressibility index etc., The results of Angle of repose and Carr's compressibility Index (%) ranged from 16-28 and 14-16, respectively which showed that blends from all the formulations having good flow property. The hardness and percentage friability ranged from 3.5-5kg/cm^2 and 0.28-0.55% respectively.

In vitro dissolution studies

Bosentan monohydrate sustained release tablets were prepared by using HPMC polymers. The release profiles of Bosentan sustained release tablets were plotted as Fig.7-9. The release rate of Bosentan mainly controlled by the hydration and swelling properties of HPMC which forms a gel layer that controls the water penetration and drug diffusion. The effect of polymer concentration on drug release could

be clearly seen from the variation of the dissolution profiles. Among all the formulations (F-1 to F-10) Contained Bosentan and HPMC K4M & HPMC K 15M Polymers in different ratios i. e., 1:0.25,1:0.5,1:1,1:1.5 and 1:2, It was found that drug release of among all the formulations, F-2 containing HPMC K 4 M in ratio of 1: 0.5 could retard drug for relatively 12 hrs compared to all other formulations. So Formulation (F-2) has showed maximum amount of drug released with drug release of 96.3 % in 12 hours, so it is chosen Optimized formulation. For matrix tablets, an 'n' value near to 0.5 indicates diffusion control and an 'n' value near to 1 indicates relaxation or erosion control. The intermediate value suggests that diffusion and erosion contributes to overall release mechanism. A value of 'n' for all matrices studied here was ranged between 0.628 to 0.894, indicating an anomalous behavior corresponding to swelling, diffusion and erosion mechanism.It was also observed that highest correlation was found for Zero order profile (R^2 > 0.934), which indicates the drug release via diffusion mechanism from hydrophilic matrices.

When the hydrophilic polymer tablets come in contact with the dissolution medium, they take up water and swell forming a viscous gel barrier. In case of hydrophilic matrix tablets, the initial swelling may aid dissolution of the freely soluble drugs, and the dissolved drug diffuses out of the swollen gel barrier into the dissolution medium. Unless the swollen gel barrier erodes, further seeping in of the dissolution medium does not occur. Thus, the release rate of the drug depends on the strength of the gel barrier i. e. the proportion of the hydrophilic polymer in the matrix tablet, its rate of hydration and viscosity.

Phenomenon of Drug Release Kinetics

The optimized formulation F2 was subjected to graphical representation to assess the kinetics of drug release. The release of drug was observed to follow the Zero order release kinetics. The initial burs effect was observed as per Zero order kinetics. Hence the drug release was mainly found to be concentration dependent. Hence we conclude that diffusion is the mechanism of drug released.

Table 4: Pre compression parameters

Formulation code	Bulk density (gr/cm3)	Tapped density (gr/cm3)	Hausner's ratio	Carr's Compressibility Index (%)	Angle of repose (Θ)
F1	0.519±0.025	0.562±0.47	1.17±0.17	14.16±0.65	23.°.47'
F2	0.577±0.048	0.526±0.49	1.75±0.52	15.91±0.54	16°.68'
F3	0.519±0.016	0.612±0.45	1.64±0.46	14.73±0.32	24°.13'
F4	0.527±0.055	0.664±0.37	1.48±0.18	15.77±0.76	22°.07'
F5	0.585±0.041	0.531±0.29	1.35±0.25	15.48±0.14	27°.98'
F6	0.554±0.036	0.556±0.74	1.46±0.47	14.35±0.45	24°.55'
F7	0.522±0.086	0.512±0.92	1.57±0.65	15.57±0.36	23°.67'
F8	0.562±0.099	0.542±0.19	1.59±0.87	14.94±0.29	26°.35'
F9	0.543±0.067	0.556±0.84	1.45±0.57	16.01±0.66	28°.46'
F10	0.511±0.026	0.547±0.97	1.41±0.45	14.65±0.43	21°.17'

All the values are expressed as mean ± S. D. (n = 3)

Table 5: Post compression parameters

Formulation code	Hardness * (kg/cm²)	Friability** (%)	Weight variation$^{\Psi}$ (mg)	Thickness$^{¥}$ (mm)	Drug Content^{Ж} (%)
F1	4.5±0.23	0.29±0.35	299.1± 1.74	3.41±0.4	99.35±0.32
F2	4.0±0.37	0.34±0.71	300.1± 1.23	3.83±0.9	99.89±0.51
F3	3.7±0.91	0.28±0.11	300.7± 1.89	3.87±0.2	98.76±0.96
F4	4.4±0.73	0.55±0.03	299.3 ± 1.33	3.42±0.1	100.21±0.13
F5	4.5±0.99	0.39±0.74	300.2± 1.98	3.64±0.7	99.43±0.73
F6	3.9±0.93	0.45±0.81	299.8 ± 1.21	3.96±0.3	98.69±0.91
F7	4.3±0.45	0.49±0.56	299.9± 1.45	3.55±0.9	100.31±0.17
F8	4.8±0.14	0.53±0.87	300.7± 1.86	3.62±0.2	99.44±0.55
F9	4.2±0.26	0.52±0.21	299.1± 1.14	3.58±0.3	100.38±0.18
F10	4.7±0.27	0.47±0.35	300.4± 1.35	3.77±0.1	99.76±0.98

All the values are expressed as mean ± S. D. * n = 6, **n =10, $^{\Psi}$n = 20, $^{¥}$ n = 6, ^{Ж} n = 2.

Table 6: Dissolution release profiles of Formulations (F1-F5)

S. No.	Time(hours)	% Cumulative drug release				
		F1	F2	F3	F4	F5
1	0	0	0	0	0	0
2	1	3.06±0.31	5.4±0.53	3.96±0.98	8.28±0.32	2.88±0.86
3	2	7.92±0.64	8.64±0.41	7.2±1.12	11.7±0.83	8.64±0.47
4	3	11.52±0.25	12.06±0.46	14.4±0.64	13.86±0.45	16.02±0.57
5	4	15.48±0.37	15.06±0.51	22.32±0.28	20.7±0.37	22.29±1.21
6	5	24.6±0.41	19.7±0.76	26.85±0.47	22.74±1.12	25.74±0.96
7	6	41.1±0.16	24.6±0.71	30.3±1.19	26.7±0.95	31.5±0.93
8	7	55.5±0.29	36.3±0.54	33.9±1.24	29.4±0.84	39.3±1.69
9	8	62.1±0.32	47.4±0.53	36.00±0.95	39.3±0.23	57.3±0.75
10	9	66.3±0.19	60.3±0.42	45.3±0.86	54.9±1.78	63.00±0.69
11	10	79.5±0.44	69.6±0.60	51.6±0.55	60.3±0.45	78.3±1.73
12	11	84.3±0.46	87.0±0.61	60.00±0.73	75.00±1.31	84.00±0.83
13	12	93.9±0.53	96.3±0.53	86.4±0.69	87.6±0.48	93.01±0.80

The data are presented as mean value ± S. D. (n = 3)

Table 7: Dissolution release profiles of Formulations (F6-F10)

S. No.	Time(hours)	% Cumulative drug release				
		F6	F7	F8	F9	F10
1	**0**	0	**0**	0	0	0
2	**1**	3.24±0.39	7.2±0.83	10.44±0.59	5.4±0.99	6.84±0.91
3	**2**	6.56±0.57	10.08±0.89	13.5±0.63	8.82±0.89	10.62±0.87
4	**3**	14.88±0.29	14.74±0.81	15.84±1.45	15.66±0.75	16.2±0.77
5	**4**	17.16±0.45	16.74±0.83	19.05±0.99	19.2±1.53	20.85±0.99
6	**5**	26.22±1.31	20.19±0.73	22.29±0.94	25.95±0.64	26.79±0.85
7	**6**	34.8±1.11	24.96±0.69	26.04±0.86	33.3±0.74	30±0.81
8	**7**	39.00±0.92	41.1±0.77	42.9±0.84	41.1±1.18	39.6±0.62
9	**8**	45.9±0.94	57.6±0.36	48.3±0.72	45±0.95	45.9±0.26
10	**9**	58.5±0.84	61.8±0.89	51±0.88	54.9±0.91	58.8±0.35
11	**10**	63.3±0.25	66.00±0.74	60±0.63	60.3±1.23	65.1±0.63
12	**11**	81.6±0.87	69.3±0.63	66±0.86	69±0.93	66±0.72
13	**12**	90.00±0.86	77.4±0.79	82.5±0.78	81±0.84	83.4±0.71

The data are presented as mean value ± S. D. (n = 3)

Table 8: Drug release kinetics studies of all formulations (F1-F10)

Formulation Code	R^2 Value				Release exponent 'n'	Mechanism of release
	Zero order	First order	Higuchi model	Korsmeyer Peppas model		
F1	0.9748	0.8544	0.8428	0.9696	1.433	Super Case II transport
F2	0.9345	0.6977	0.7651	0.9595	0.922	Non- fickian diffusion
F3	0.9313	0.7078	0.8074	0.9826	1.174	Super Case II transport
F4	0.9298	0.7656	0.7807	0.9727	0.676	Non- fickian diffusion
F5	0.9716	0.8220	0.8313	0.9866	1.314	Super Case II transport
F6	0.9700	0.8025	0.8271	0.9879	1.322	Super Case II transport
F7	0.9558	0.9170	0.8293	0.9180	0.805	Non- fickian diffusion
F8	0.9589	0.8419	0.8346	0.8586	0.628	Non- fickian diffusion
F9	0.9874	0.8910	0.8671	0.9856	1.054	Case II transport
F10	0.9778	0.8652	0.8573	0.9865	0.894	Non- fickian diffusion

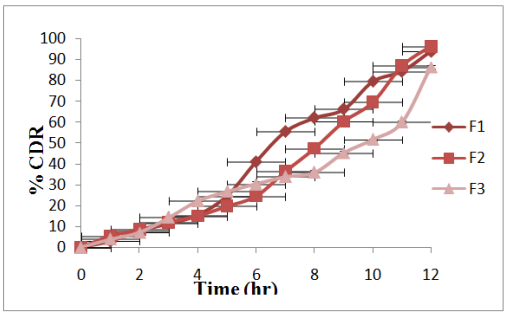


Fig. 10: Dissolution profiles of Formulations F1-F3 (Using HPMC K4M)

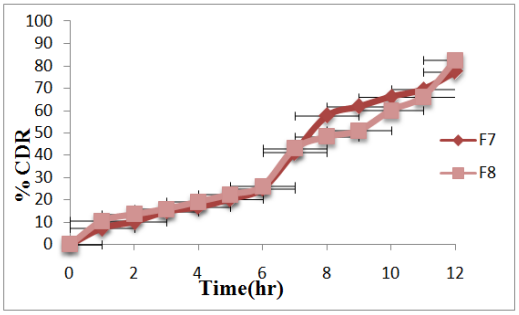


Fig. 12: Dissolution profiles of Formulations F7, F8 (Using HPMC K 15M)

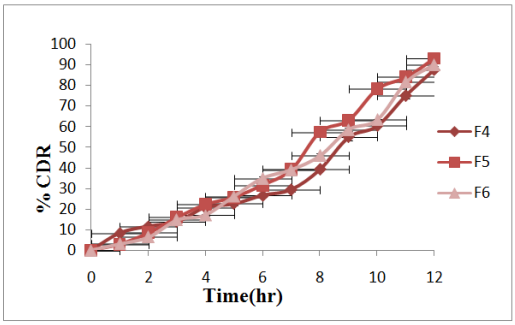


Fig. 11: Dissolution profiles of Formulations F4-F6 (Using HPMC K 4M & K 15M)

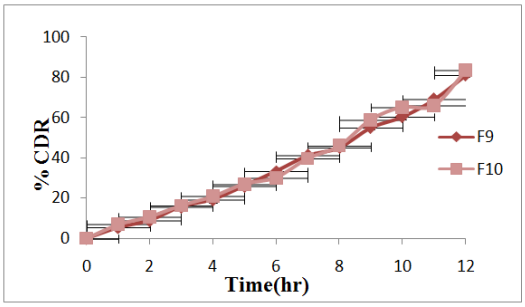
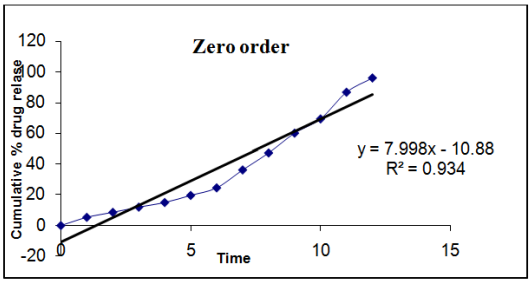
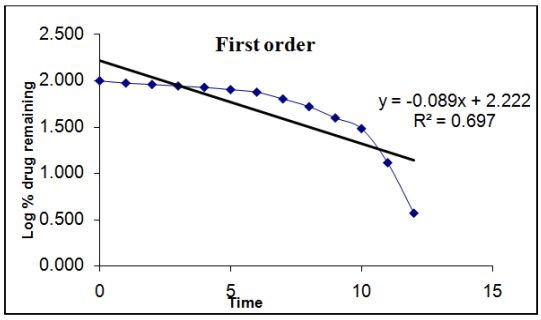
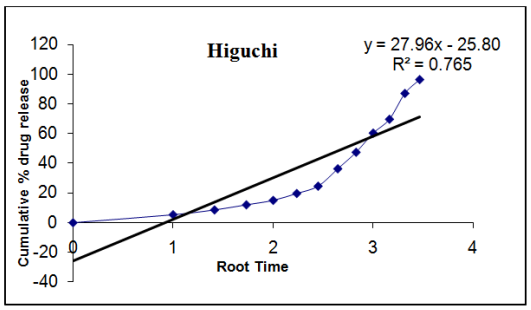


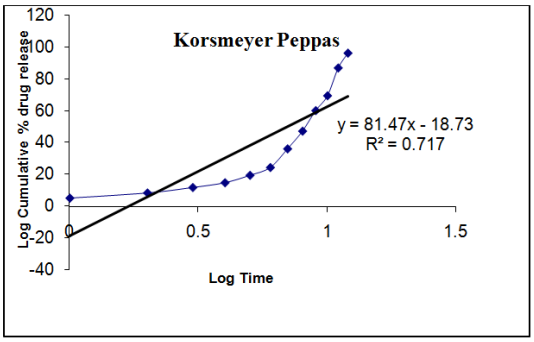
Fig. 13: Dissolution profiles of Formulations F9, F10 (Using HPMC K 15M)

Release Kinetics of Optimized formulation F2









CONCLUSION

From the present study, the following conclusions can be drawn:

❖ The purpose of the present study was to formulate and evaluate sustained release matrix tablets of Bosentan was prepared by wet granulation method by using different polymers of hydroxy propyl methyl cellulose grades.

❖ Successfully using HPMC polymer of different viscosity. According to *in vitro* release studies, the release rate was decreased with increasing viscosity and amount of polymer.

❖ IR spectra indicated the absence of probable chemical interaction between the drug and polymers used in different proportions.

❖ DSC thermograms obtained for the pure drug and drug + different polymers indicated that there is no interaction for drug and polymers and suggested the good miscibility of the drug and polymers.

❖ *In-vitro* dissolution studies showed that tablets of Bosentan in 1:0.5 proportion, prepared by wet granulation is the best to increase sustain effect due to the polymer concentration.

❖ All the formulations fulfill the official limit for Physicochemical parameters like weight variation, hardness, friability and drug content uniformity.

❖ The optimized formulation of F2 gave the best in vitro release of 96.3±0.53 in 12 hrs in simulated intestinal fluid. The release of drug followed matrix diffusion mechanism.

❖ Hence it is concluded that among the Ten formulations of Bosentan, F-2 formulation containing Drug to polymer (HPMC K 4 M) in ratio 1:0.5 is optimized based on its ability to sustain drug release till 12 hours in simulated intestinal fluid. The results of the study clearly demonstrated that HPMC matrix tablet formulation is an effective and promising drug delivery system for once a daily administration of Bosentan.

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CONFLICT OF INTERESTS

Declared None

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