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FORMULATION AND EVALUATION OF CONTROLLED RELEASE TABLETS OF BOSENTAN

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ABSTRACT

In the present research, an attempt has been made to formulate controlled release matrix tablets of Bosentan. Bosentan is used to treat pulmonary arterial hypertension (PAH). It improves your ability to exercise and prevents your condition from getting worse. Different formulations were prepared by using different polymers like HPMC 50 CPS, HPMC E-5, karaya gum; Avicel PH102, PVP K30, Hydroxy Ethyl Cellulose and Talc etc. with different ratios were used in the development of formulations. HPMC 50 CPS, HPMC E-5 and karaya gum are used as rate controlling polymer, PVP K30 used as binder, microcrystalline cellulose as filler. The prepared tablets were evaluated for pre compression and post compression parameters with different ratios. All the evaluated parameters of the formulations showed compliance with pharmacopoeial standards. The selected formulations were subjected to stability studies as per ICH guidelines at different temperature and humidity conditions. It can be concluded that among all the formulations and the combinations of HPMC 50CPS, HPMC E-5, Avicel PH102 considered as the optimized formulations in the present research work. The optimized formulations show non-fickian diffusion mechanism of release and other all evaluation.

KEYWORDS: Bosentan, HPMC 50 CPS, HPMC E-5, Karaya gum, Avicel PH102, PVP

K30 and Magnesium stearate etc.

INTRODUCTION

The controlled release system is to deliver a constant supply of the active ingredient, usually at a zero-order rate, by continuously releasing, for a certain period of time, an amount of the drug equivalent to the eliminated by the body. An ideal controlled drug delivery system is the one, which delivers the drugs at a predetermined rate, locally or systemically, for a specific period of time.

The aim of this present work is to formulate a controlled release matrix tablet of Bosentan preparation and evaluation using various polymers such as HPMC 50 CPS, HPMC E-5 and Karaya gum.Bosentan is a dual endothelin receptor antagonist important in the treatment of pulmonary artery hypertension (PAH). It is licensed in the United States, the European Union and other countries by Actelion Pharmaceuticals for the management of PAH under the trade name Tracleer®. Bosentan is used to treat pulmonary hypertension by blocking the action of endothelin molecules that would otherwise promote narrowing of the blood vessels and lead to high blood pressure.

MATERIALS AND METHODS

Bosentan obtained as a gift sample from Spectrum Pharma Labs, Hyderabad, Karaya Gum was obtained from Himedia Laboratory, Mumbai. HPMC 50 CPS, HPMC E5, PVP K30 was obtained from Nice Chemicals Laboratory, Mumbai. Magnesium Stearate, Micro Crystalline Cellulose and all other chemicals and solvents used are from Spectrum Pharma Labs, Hyderabad.

Evaluation Parameters

Pre Compression Parameters

Precompression parameters include bulk density, tapped density, compressibility index and Hausner's ratio, angle of repose, total porosity and flow rate.

Post Compression Parameters

A. Thickness and diameter

Control of physical dimension of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using Vernier calipers. It is measured in mm.

B. Hardness

The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in Kg/cm^2.

C. Friability (F)

Tablet strength was tested by Friabilator USP EF-2. Pre weighed tablets were allowed for 100 revolutions (4min), taken out and were dedusted. The percentage weight loss was calculated by rewriting the tablets. The % friability was then calculated by,

$$F = \frac{(W_{initial}) - (W_{final})}{(W_{intial})} \times 100$$

D. Weight variation test

The weight of the tablet being made in routinely measured to ensure that a tablet contains the proper amount of drug. The USP weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablet meet the USP test if not more than 2 tablets are outside the percentage limits and if no tablets differs by more than 2 times the percentage limit. USP official limits of percentage deviation of tablet are presented in the following table,

$$PD = \frac{(W_{avg}) - (W_{initial})}{(W_{avg})} \times 100$$

Where, PD = Percentage deviation, $W_{aBosentan}$ = Average weight of tablet, $W_{initial}$ = individual weight of tablet.

E. Uniformity of drug content.

Five tablets of various formulations were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in Phosphate buffer pH 6.8, the drug content was determined measuring the absorbance at 274nm after suitable dilution using a UV/Visible Spectrophotometer (UV-1800).

In-vitro release study

Apparatus : USP XXIV dissolution testing apparatus II

(Paddle method)

Dissolution medium	:	Phosphate buffer pH- 6.8		
Temperature	:	37± 0.5^{0}C RPM	:	50
Vol. withdrawn and replaced	:	5ml every 1 hour		
λ max	:	274		
Blank solution	:	Phosphate buffer pH- 6.8		
Duration of study	:	12 hours		
Volume of dissolution media	:	900ml		

Procedure

The release rate of Bosentan from tablets was determined using The United States Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle type). The dissolution test was performed using 900 ml of pH 1.2, for first 2 hours then in phosphate buffer pH 6.8 for rest of the hours at 37±0.5^{0}C and 50 rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 hours and the samples were replaced with fresh dissolution medium. Cumulative percentage of drug release was calculated.

Kinetic Analysis of In-Vitro Release Rates of Controlled Release Tablets

The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows:-

1. Zero – order kinetic model – Cumulative % drug released versus time.
2. First – order kinetic model – Log cumulative percent drug remaining versus time.
3. Higuchi's model – Cumulative percent drug released versus square root of time.
4. Korsmeyer equation / Peppa's model – Log cumulative percent drug released versus log time.

Table-1: Tablet composition of different formulations of Bosentan matrix tablets containing HPMC 50 CPS as controlled release polymer

Ingredients (mg)	Formulation Code					
	F1	F2	F3	F4	F5	F6
Bosentan	16	16	16	16	16	16
HPMC 50 CPS	61	56	51	46	41	36
PVP K30	10	10	10	10	10	10
Micro crystalline cellulose	35	35	35	35	35	35
Hydroxy ethyl cellulose	15	15	15	15	15	15
Metolose SR	-	5	10	15	20	25
Mg stearate	8	8	8	8	8	8

talc	5	5	5	5	5	5
Total weight(mg)	150	150	150	150	150	150

Table-2: Tablet composition of different formulations of Bosentan matrix tablets containing HPMC E5 as controlled release polymer

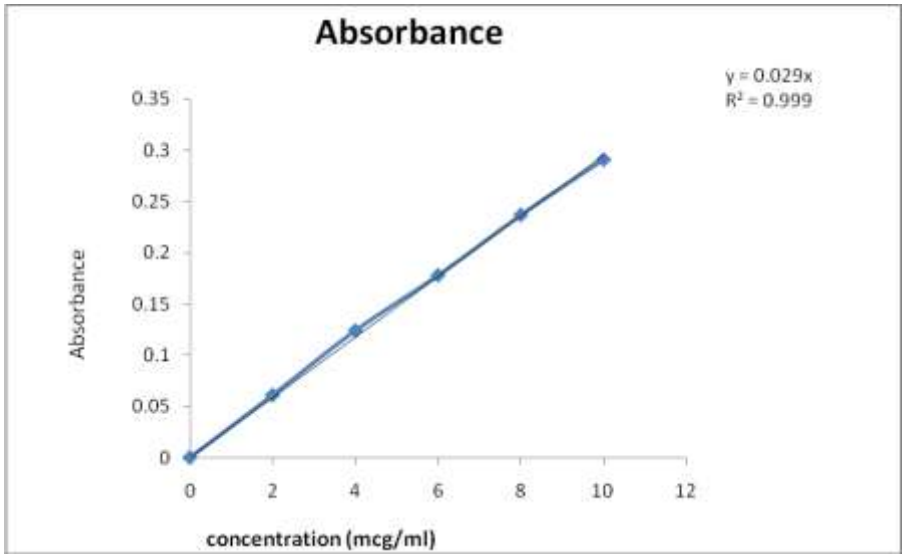
Ingredients (mg)	Formulation Code			
	F7	F8	F9	F10
Bosentan	16	16	16	16
HPMC E5	51	46	41	36
PVP K30	10	10	10	10
Micro crystalline cellulose	35	35	35	35
Hydroxy Ethyl cellulose	15	15	15	15
Metolose SR	10	15	20	25
Mg stearate	8	8	8	8
talc	5	5	5	5
Total weight(mg)	150	150	150	150

Table 3: Tablet composition of different formulations of Bosentan matrix tablets containing karaya gum as controlled release polymer

Ingredients (mg)	Formulation Code		
	F11	F12	F13
Bosentan	16	16	16
Karaya gum	15	20	35
PVP K30	10	10	10
Microcrystalline cellulose	25	25	25
Hydroxy Ethyl cellulose	20	25	20
Metolose SR	51	41	31
Mg stearate	8	8	8
Talc	5	5	5
Total weight(mg)	150	150	150

RESULTS AND DISCUSSION

Standard curve of Bosentan



Melting Point Determination

Melting point of Bosentan was determined by capillary method. The melting point of Bosentan was found to be in the range 198° which compiled with BP standards, indicating purity of the drug sample**.**

Solubility

Bosentan was found to be more soluble in pH 6.8 phosphate buffer as compare to pH1.2 and pH 7.4 phosphate buffer, i.e. it has optimum solubility at pH 6.8 (4.87 mg/ml). The solubility decrease to about (2.57mg/ml) at pH 1.2 and it was equal to (3.36 mg/ml) at pH 7.4.

Compatibility Study

Compatibility study is important to understand the interaction between the drug and polymers. It saves costs and it makes easier to choose a few excipients from the long list of excipients for a better formula.

Drug- excipient interactions play a vital role with respect to release of drug from the formulation amongst others. FTIR techniques have been used here to study the physical and chemical interaction between drug and excipients used. In the present study, it has been observed that there is no chemical interaction between drug and the polymers used.

The peaks obtained in the spectra's of each polymer correlates with the peaks of drug

spectrum. This indicates that the drug was compatible with the formulation components.

Flow Properties

A flow property plays an important role in pharmaceuticals especially in tablet formulation because improper flow may cause more weight variation. Values of Carr's Index (Compressibility) below 15% usually give rise to good flow properties but readings above 25% indicate poor flow properties. It was found that the compressibility values of the powders were below 15% and hence they exhibit good flow characteristics.

Values of angle of repose are rarely 20^0 and values up to 40^0 indicate reasonable flow properties. Above 50^0 however the powder flows only with great difficulties. Dynamic angle of repose measurements can be replicated with relative standard deviations of approximately 2%. They are particularly sensitive to changes in particle size distribution and to the moisture content and they provide a rapid means of monitoring significant batch to batch differences in these respects.

The Carr's Index (Compressibility) of the powders was in the range of 6.68 to 12 .60. The angles of repose of the powders were in the range of 25.39^0 to 28.76^0, which indicate a good flow property of the powders. Here the angle of repose was found to be below 40^0 this shows that the reasonable flow property of powders.

Evaluation of Tablets

Physical Parameters (Shape, Size, Hardness & Friability)

The punches used to compress the tablets were 9mm, spherical shaped. The shape and size of the tablets were found to be within the limit. The hardness of the tablets was found to be in the range of 4.10 to 4.46 Kg/cm^2. Thicknesses of the tablets were found to be in the range of 3.98 to 4.24 mm. The friability of the tablets was found to be less than 1% and it was within the range of standard specification.

Weight Variation and Drug Content

Weight variation test helps to check whether the tablet contain proper quantity of the drug. From each of the formulations ten tablets were randomly selected and weighed. The results are given in detail. The average weights of the tablets were found to be within the prescribed official limits (IP).

Drug content for each of the formulations were estimated. The drug content for all the

batches were found to be in the range of 97.12 to 99.78%.

In-Vitro Release Study

All the 13 formulation of prepared tablets of Bosentan were subjected to in vitro release studies, these studies were carried out using dissolution medium, (pH 1.2 and Phosphate buffer pH 6.8).by using USP-2 (paddle type) dissolution apparatus. The results were evaluated for 12 hours. As per the results of dissolution study formulations F-1, F-2, F-3, F-4, F-5, F-6, F-7, F-8, F-9, F-10, F-11, F-12 and F-13, showed 92.36%,82.93 %, 85.36%, 89.22%, 93.26%, 92.53%, 94.53%, 90.16%, 94.31%, 92.51%, 83.66%, 81.03%, release respectively over a period of 12 hours.

Among all the formulation, F-5, showed 93.26%, release respectively at the end of 12 hours.

Table 4: Percentage drug release of formulations F1-F6

Sr. No.	Time (hrs)	FORMULATION CODE					
		F1	F2	F3	F4	F5	F6
In acidic buffer pH 1.2							
1	0	0.0	0.0	0.0	0.0	0.0	0.0
2	1	9.13	8.04	7.51	6.12	5.55	5.06
3	2	15.17	13.21	10.9	9.65	8.66	7.52
In phosphate buffer pH 6.8							
4	3	19.35	18.44	17.87	16.33	15.55	14.11
5	4	23.18	22.13	21.32	20.69	19.32	18.25
6	5	32.13	31.25	29.24	28.63	27.17	25.64
7	6	42.21	40.09	37.85	35.23	33.23	30.08
8	7	56.53	55.32	49.44	47.52	44.39	41.36
9	8	72.5	69.25	59.32	58.65	43.32	54.25
10	9	81.36	75.25	70.02	69.31	67.04	63.27
11	10	92.36	89.23	85.36	78.32	72.02	71.3
12	11				89.22	84.11	80.05
13	12					93.26	89.63

Table 5: Percentage drug release of formulations F7-F13

SN. No.	Time (hrs)	FORMULATION CODE						
		F7	F8	F9	F10	F11	F12	F13
In acidic buffer pH 1.2								

1	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2	1	13.66	12.28	10.2	9.23	7.67	6.65	5.40
3	2	21.65	19.58	18.55	17.57	12.52	8.56	9.52
In phosphate buffer pH 6.8								
4	3	30.98	27.56	25.23	24.31	21.55	18.23	15.28
5	4	42.50	36.88	32.63	30.63	27.32	24.56	20.33
6	5	54.58	48.26	42.53	40.58	32.23	30.67	28.07
7	6	69.37	61.33	52.47	49.5	43.92	38.57	36.01
8	7	81.56	78.23	73.14	60.27	51.27	44.01	40.54
9	8	92.53	87.41	83.12	74.28	66.5	52.21	49.23
10	9		94.53	90.16	85.23	74.22	59.59	55.44
11	10				94.31	82.51	66.54	63.61
12	11					88.26	74.14	69.02
13	12					92.51	83.66	81.03

Kinetics

Different models like Zero order, First order, Higuchi's and Krosmeyers-peppas plots were drawn. The regression coefficient (R^2) value for Zero order, First order, Higuchi's and Krosmeyers-peppas plots for formulation F5 were found to be 0.977, 0.813, 0.967, 0.583, 0.718(n value). The optimized formulations F-5 follow Zero order and higuchi release mechanism

CONCLUSION

In this study matrix tablet of Bosentan were prepared by including analytic control of the production process and preparation and isolation mixture of 1-haloacetyl-2(S)-pyrrolidine carboxamide, using HPMC 50CPS, HPMC E-5 and karaya gum, PVP K30 polymers as retardant. The drug-polymer ratio was found to influence the release of drug from the formulations. It was found that increase in the concentration of HPMC 50CPS in polymeric ratio decreases the drug release. The formulations F-5 showed good drug release with good matrix integrity release of 93.26% at the end of 12hr so the formulation F-5 selected as the optimized formula. The enteric coated polymer was used to avoid the drug release in stomach because the drug is quiet unstable in stomach and the aim of the work is to release the drug in intestine. The formulation F-5 showed good drug release with good matrix integrity. Different parameters like hardness, friability, weight variation, drug content uniformity, in-vitro drug release were evaluated. Based on these results formulation F-5was found to be the most promising formulations. The regression coefficient (R^2) of Higuchi plot of optimized formula F-5 shows that the drug releases through the matrix was diffusion and

slope (n) value of peppas plot confirms that non-Fickian diffusion (anomalous transport) was the main mechanism. The regression coefficient (R^2) values of zero order of the optimized formulation F-5 was greater than the R^2 values of first order. Thus, the drug release follows zero order release kinetics.

The results suggest that the developed controlled-release matrix tablets of Bosentan could perform better than conventional dosage forms, leading to improve efficacy and better patient compliance. Thus the aim of this study was achieved. Further preclinical and clinical studies are required to evaluate the efficacy of these formulations of Bosentan in the management of hypertensive.

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