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Research Article

Formulation, Development and Evaluation of Bilayer Floating Tablets of Antihypertensive Drug Bosentan

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Abstract

Hypertension, or high blood pressure, is a major public health concern around the world because of its large contribution to the global health burden and its function as a major risk factor for a variety of disease processes. Bosentan SR Floating Bilayer Tablets were made with HPMC K4M, HPMC E-15, and HPMC E-15 alone (80%) and in combination with varying percentages of polymer (20&60 percent, 40&40 percent, and 60&20 percent). The hydrophilic polymer HPMC is used to make three different formulations (M4, M8, and M12) of floating Bosentan SR tablets, each with a viscosity grade of 80 percent. M12 formulation was shown to be suitable for SR tablet formulation. From the M12 formulation. It's based on the M12 formula. The fraction of high viscosity polymer can be lowered by adding low viscosity polymer, as demonstrated in the C3 formulation. It was clear from the dissolution profile of formulation C3 that by mixing the low and high viscosity polymers, the drug release from the formulation may be improved as compared to manufacturing M12 high viscosity polymer alone. According to the findings of this investigation, as floating duration increases, the release rate drops. As a result, it's appropriate for long-term formulation.

Keywords: Bosentan, Floating Bilayer Tablets, Hypertension, SR Tablets, HPMC K4M, E-15

1. INTRODUCTION:

Hypertension, or high blood pressure, is a major public health concern around the world because of its large contribution to the global health burden [1] and its function as a major risk factor for a variety of disease processes. In the year 2019, high blood pressure was responsible for 54% of strokes, 47% of ischemic heart disease, 75% of hypertensive disease, and 25% of all cardiovascular disease worldwide. Hypertension has a demonstrable negative influence on health, especially when considering the disability, reduced quality of life, and mortality associated with stroke and cardiovascular disease [2]. Hypertension has a demonstrable negative influence on health, especially when considering the disability, reduced quality of life, and mortality associated with stroke and cardiovascular disease. Systolic blood pressure of more than 115 mmHg was responsible for 7.6 million fatalities (13.5 percent of all deaths) and 92 million disability life-years (6 percent of total) in 2019. It's disheartening to learn that such widespread negative consequences are linked to a preventable cause [3].

For the chronic treatment of many disorders, the oral route has been the most common route of medication delivery [4]. The goal of this study was to use an optimization technique to generate an optimum bilayer tablet for anti-hypertension patients utilizing a hypertensive agent as a model drug candidate. For the treatment of hypertension, combination drug therapy is advised because it allows drugs with distinct mechanisms of action to complement each other and effectively lower blood pressure at lower than maximum dosages of each [5].

Any drug delivery system's purpose is to deliver a therapeutic amount of medicine to the appropriate spot in the body in order to establish and then maintain the correct drug concentration quickly. The spatial placement and temporal distribution of medicine are the two most significant components of drug delivery [6]. Drug targeting to a specific organ or tissue requires spatial positioning. Controlling the rate of drug delivery to the target tissue is referred to as temporal delivery. The goal of this study was to create an optimal GFDDS [7] with sustained and immediate release—a peroral intragastric floating dose form with a bulk density lower than gastric fluids and the ability to float on stomach contents.

Independent formulation variables such as total polymer content-to-drug ratio, polymer-to-polymer ratio, and different viscosity classes of polymers will be used to achieve the goals [8].

2. MATERIAL AND METHODS

PreparationofReagents

Preparation of 0.1N HCL

8.5 ml of Con.HCl dissolved in 1000ml of distilled water to prepare a 0.1N HCl.

Simulated Gastric Fluid pH 1.2

The solution was made up of 0.2 g sodium chloride and 0.7 ml concentrated hydrochloric acid, 1000 ml distilled water, and sodium hydroxide solution to set the pH to 1.2.

Absorption Maxima and Standard Plots

Preparation of Absorption maxima for Bosentan using pH 1.2 simulated gastric fluid.

Bosentan (100 mg) was accurately weighed and dissolved in a tiny amount of stimulated gastric fluid pH 1.2, then diluted to 100 ml with the same solvent. The stock solution includes 1 mg of Bosentan per mL. Different working standard solutions, i.e., 10, 20, 30, 40, and 50 g/ml, were prepared from this stock solution with stimulated stomach fluid pH 1.2 and the absorbance was measured at 232nm using simulated gastric fluid as a blank utilizing UV spectroscopic method47. Concentration was plotted on the X-axis and absorbance was plotted on the Y-axis to create a graph. Absorption maxima and UV spectrum of Bosentan.

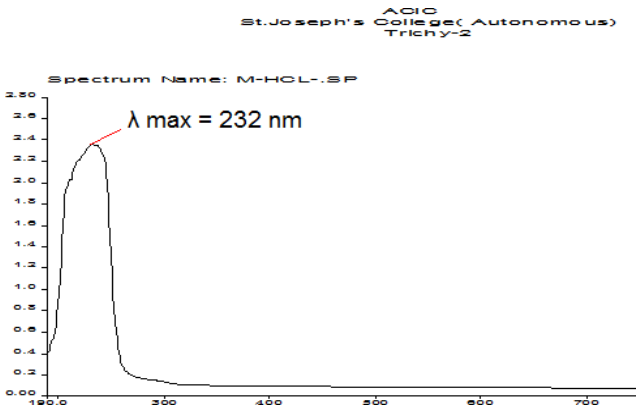

Figure 1: Absorption maxima and UV spectrum of Bosentan

Standard Plot

The Standard plot of Bosentan in simulated gastric fluid pH 1.2

Table 1: The Standard plot of Bosentan

S.No	Concentration µg/ml	Absorbance at 232nm
1	0	0
2	10	0.2897
3	20	0.5371
4	30	0.8484
5	40	1.118
6	50	1.39

RESULTS AND DISCUSSION

Preformulation studies

Description

Bosentan: White to off white crystalline powder

Drug- Excipient Compatibility Studies by FT-IR analysis

FT-IR analysis was used to determine drug-excipient compatibility [9]. The IR spectrum of the pure medication, Bosentan, as well as excipients such as HPMC K4M, HPMC E-5, and HPMC E-15, was first acquired. Following that, IR spectra were obtained from various drug admixtures with additional excipients such as Bosentan, HPMC K4M, HPMC E-5, and HPMC E-15. Major peaks in the spectra of physical admixtures were identified and recorded..

C-N stretching was observed at 3303.04 and C-H stretching at 2692.21 in the Bosentan drug, while C-N stretching was observed at 3289.10, C-H stretching at 2856.80, and C-H(out of plane) at 798.49 in the combination of both medications (Bosentan).

In Bosentan, C-H stretching was observed at 3171.90. When Bosentan and Polymer were combined, C-H stretching was observed at 2939.64, 2944.65, 2940.92, and C-H aliphatic stretching was observed at 2213.68, 2497.21, 2202.74.

In Bosentan, N-H stretching was observed at 3376.04 in a mixture of Metformin HCl and Polymer, and the same group was observed in N-H stretching at 3375.06, 3385.45, 3383.44 C=S stretching at 1442.18, 1446.64,1451.54. C-H out of the plane at 931.65 was observed in Bosentan. When Bosentan and Polymer were combined, the same group was observed in C-H out of the plane at 936.80, 939.58,937 S=O stretching at 1351.27.

Table 2: IR Spectral assignment of Bosentan

S.no	Wavenumber (cm^{-1})	Assignment
1	3173.06	N-H stretching
2	2687.10	C-H stretching
3	1629.52	C=O stretching
4	1573.03	C-N stretching
5	1168.15	C-C stretching
6	931.12	C-H out plane bending

Evaluation Parameter

Evaluation of granules of Floating Bosentan SR

Pre-Compression parameters were applied to the produced granules, and the results were found to be within acceptable limits (Carr's index of 15% indicates excellent compressibility, Angle of repose of 25°, and Hausner's ratio of 1.25 shows good flow property) [10]. The granules' results were shown in table no (3).

Table 3: Precompression parameters of Floating Bosentan SR

Formulation batch code	The Angle of repose (°) ± S.D	Bulk density (gm) ± S.D	Tapped density (gm) ± S.D	Carr's Index (%) ±S.D	Hausner's Ratio ± S.D
M4	23.98±0.3	0.49±0.05	0.59±0.01	14.82±0.56	1.02±0.4
M8	24.34±0.2	0.54±0.03	0.61±0.03	13.92±0.67	1.04±0.3
M12	26.59±0.4	0.56±0.02	0.62±0.02	15.01±0.28	1.11±0.6

S.D = Standard Deviation, n=3

Physical Evaluation of Floating Bosentan SRtablet

All of the trial batch's prepared tablets (M4, M8,&M12) are within the Pharmacopoeial limits. The weight uniformity is 0.640-0.690g, friability is 0.3-0.5 percent, drug content is 98.98-99.99 percent, hardness is 4-6 kg/cm2, and the floating lag time is 29,28&25 seconds. The M4&M8 formulations reveal that the low viscosity grade polymer HPMCE-15 has the longest floating lag time, while the M12 formulation shows that the high viscosity polymer HPMCK4M has the shortest floating lag time [11]. The results are tabulated in the table below (4).

Table 4: Physico – Chemical Characteristics of Floating Bosentan SR

Formulation batch code	The Average weight of tablets (gm) ± S.D	Hardness (Kg/cm²) ± S.D	Friability (%) ± S.D	Drug content (%)± S.D	Floating lag time (Secs)	Total buoyancy time (Hrs)
M4	0.651 ±0.41	4.2±0.24	0.29±0.05	98.26±0.21	29	20
M8	0.649±0.32	4.8±0.31	0.3±0.04	98.99±0.13	28	20
M12	0.650±0.21	4.1±0.42	0.2±0.03	99.99±0.15	25	20

S.D = Standard Deviation, n=3

Table 5: Determination of Swelling index for Floating Bosentan SR Tablets

Time (hrs)	Formulation code		
	M4	M8	M12
1	50.83±0.5	56.55±0.2	65.50±0.26
2	52.44±0.4	68.74±0.7	86.75±0.75
3	61.12±0.1	78.56±0.6	97.82±0.28
4	79.03±0.3	90.52±0.5	109.89±0.9
5	95.23±0.26	105.23±0.3	128.55±0.5

The increased swelling index in formulation M12 is owing to the polymer's viscosity, which has a significant impact on the swelling process. From the above, it is obvious that tablet swelling increases as time passes because the polymer gradually absorbed water due to its hydrophilic nature and swelled [12]. As the viscosity of the polymer increases, the water absorption rate increases. Finally, the polymer with the highest viscosity has the most absorption. No. 1 was shown in the table above.

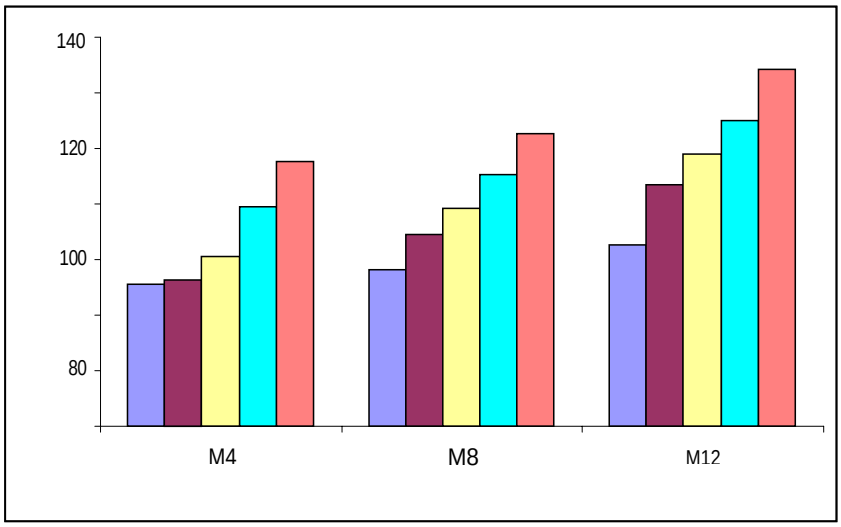

Figure 2: Determination of Swelling index for Floating Bosentan SR Tablets

In vitro drug release profile

The *in vitro* drug release study was carried out by using USP dissolution apparatus II (paddle type) [13] and results were tabulated in a table (6).

Table 6: *In vitro* drug release of Floating Bosentan SR

Time (hrs)	Cumulative % of drug released (±S.D)		
	M4	**M8**	**M12**
0	0	0	0
0.25	4.31±0.31	5.07±0.73	6.59±0.52
0.5	9.66±0.60	9.15±0.12	14.55±0.58
1	13.54±0.54	13.01±0.14	18.59±0.54
2	18.85±0.86	17.82±0.86	27.96±0.94
4	24.15±0.12	22.46±0.42	33.11±0.19
6	30.57±0.56	27.28±0.29	41.24±0.26
8	37.99±0.98	31.03±0.34	47.13±0.14
10	43.31±0.31	36.17±0.13	53.98±0.96
12	48.92±0.99	40.98±0.92	61.18±0.12
14	53.68±0.67	49.69±0.63	67.24±0.24
16	61.79±0.75	54.33±0.34	75.67±0.64
18	66.09±0.96	60.78±0.76	83.24±0.23
20	70.8±0.82	66.19±0.18	**86.12±0.19**

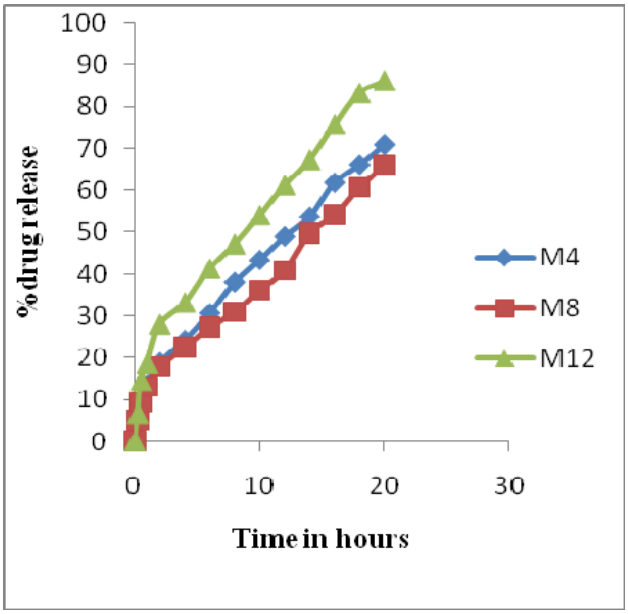

Figure 3: *In vitro* drug release profile of Floating Bosentan SR

The drug released at the end of 20 hours was determined to be 70.8 percent, 66.19 percent, and 86.12 percent, respectively, according to the in vitro profile for Bosentan SR (M4, M8,&M12). Based on this release profile, it was clear that the formulation M12 was appropriate for SR formulation. (The formulations M4 and M8 did not meet the USP SR limit of NLT 80 percent released after 20 hours.).

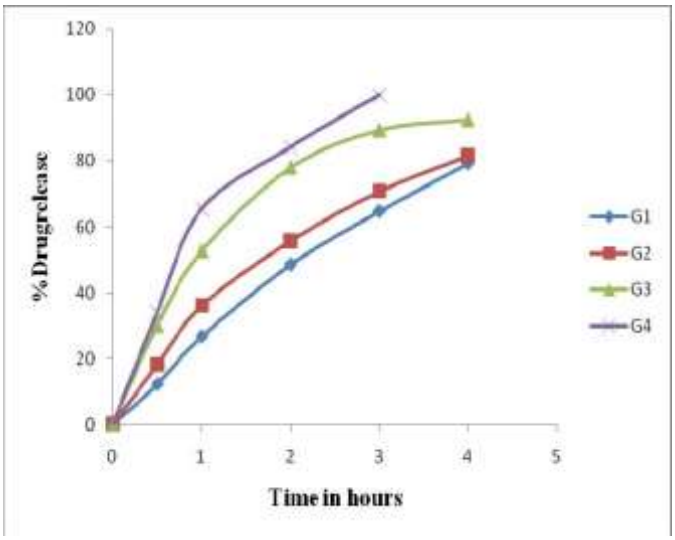

Figure 4: *In-vitro* Profile of Immediate release (G1-G4)

From the *in vitro* profile for formulation G1-G4 the drug released was found to be 64.78%, 70.83%, 89.34% & 99.95% at the end of 3 hrs. From the release profile, G4 was suitable for IR formulation.

Evaluation of Floating Bilayer tablet of Bosentan

The results of pre-compression parameters for different formulation batches of the Floating Bilayer tablet of Bosentan tablet were shown in the table.

Table 7: Precompression Parameters of Floating Bilayer tablet of Bosentan

Formulation batch code	The Angle of repose (°) ± S.D	Bulk density (gm) ± S.D	Tapped density (gm) ± S.D	Carr's Index (%) ± S.D	Hausner's Ratio ± S.D
C1	25.65±0.02	0.52±0.02	0.49±0.02	13.93±0.3	1.11±0.02
C2	26.93±0.3	0.54±0.04	0.54±0.34	14.92±0.5	1.19±0.1
C3	28.45±0.2	0.56±0.21	0.58±0.43	14.98±0.2	1.05±0.01
C4	24.78±0.08	0.51±0.31	0.52±0.02	12.93±0.02	1.12±0.03
C5	23.24±0.03	0.58±0.81	0.51±0.04	14.82±0.08	1.18±0.02
C6	23.67±0.34	0.49±0.09	0.59±0.03	15.92±0.72	1.12±0.2
C7	24.73±0.34	0.52±0.01	0.62±0.06	14.92±0.04	1.13±0.1
C8	23.94±0.02	0.56±0.2	0.68±0.34	13.92±0.05	1.16±0.4
C9	22.82±0.4	0.58±0.02	0.64±0.56	14.02±0.4	1.15±0.5

S.D = Standard Deviation, n=3

Physico – Chemical Characteristics of Floating Bilayer tablet of Bosentan

The results of physicochemical characterization of different formulation batches of Floating Bilayer tablets were summarized in table no (8). The results show that the formulation C1-C9 lies within IP limits weight variation, Hardness, Friability, and Drug content.

Table 8: Physico – Chemical Characteristics of Floating Bilayer tablet of Bosentan

Formulation batch code	The average weight of tablets (g) ± S.D	Hardness (Kg/cm^2) ± S.D	Friability (%) ± S.D	Drug content (%) ± S.D	Floating lag time (Secs)	Total buoyancy time (Hrs)
C1	0.650±0.23	4.4±0.8	0.2±.02	97.98±0.25	25±0.2	19±0.12
C2	0.649±0.22	4.8±0.6	0.3±0.04	98.99±0.52	26±0.23	20±0.34
C3	0.651±0.23	4.8±0.82	0.2±0.01	99.99±0.9	25±.18	20±0.24
C4	0.651 ±0.14	4.2±0.2	0.29±0.06	98.26±0.41	28±0.01	21±0.56
C5	0.654±0.23	5.32±0.3	0.3±0.01	96.99±0.6	27±0.85	20±0.9
C6	0.650±0.11	5.1±0.5	0.2±0.02	99.99±0.12	30±0.12	21±0.2
C7	0.654±0.42	5.2±0.12	0.26±0.03	97.67±0.23	32±0.45	21±0.1
C8	0.652±0.2	4.4±.12	0.24±0.01	98.23±0.45	29±0.38	22±0.8
C9	0.653±0.3	4.2±.9	0.04±0.12	97.34±0.56	30±0.64	24±.9

S.D = Standard Deviation, n=3

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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