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Formulation Development and *In-vitro* Evaluation of Bosentan Gastroretentive Drug Delivery System

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A B S T R A C T

The present investigation of the development of floating tablets are used in the treatment of high blood pressure in the lungs (pulmonary arterial hypertension). The Bosentan floating tablets were prepared by direct compression method. The evaluation of Precompression Blend Flow Properties of the granules of angle of repose shows the F1 to F9 20.60 θ to 29.50θ, Bulk density shows the F1 to F9 value was found to be 0.43 g/cc to 0.45 g/cc, compressibility index shows the F1 to F9 value was found to be 11.7 % to 15.3 %. The prepared Bosentan floating tablets such as thickness, hardness, weight variation, friability. The optimized formulation F7 contains the average thickness of 3.05mm, average hardness of 7.1 kg/cm^2, friability of 0.12%, the buoyancy studies of the bosentan floating tablets show 5 mints to 13 mints & the total floating time of tablets 8 to more than 12 hours. The swelling index of floating tablet 124 mins. The *In vitro* dissolution studies of floaing tablets of best formulation F7 shows 99% Drug release bosentan floating tablets within 12 hours. The best formulation F7 performs the Kinetic models like zero, first, higuchi, krosmeyer peppas.

Keywords: Gastro retentive floating tablets, Bosentan, buoyancy studies.

A R T I C L E I N F O

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1. Introduction

To prepare and evaluate floating tablets of Bosentan that retains the dosage form in the stomach. To provide an increased gastric residence time resulting in prolonged drug delivery in gastrointestinal tract using HPMC different

grade and Guar gum, Ethyl Cellulose as sustain release polymers. To study the various formulations and process variables that ultimately affects the drug release [1]. To selection and optimization of polymer concentration, type of filler and amount of polymer that has pronounced effect on tablet properties and drug release profile as well as buoyant properties of the formulations. The present investigation applied a systematic approach to the development of floating drug delivery system It is used to treat high blood pressure in the lungs (pulmonary arterial hypertension) [2]. It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time i.e., gastro retentive dosage forms. The GRDFs extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form [3].

Advantages of Floating tablets [4]**:**

Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. These advantages include:

1. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
2. Controlled delivery of drugs.
3. Delivery of drugs for local action in the stomach.
4. Treatment of gastrointestinal disorders such as gastro-esophageal reflux.
5. Simple and conventional equipment for manufacture.
6. Ease of administration and better patient compliance.

Disadvantages of Floating tablets [5] **:**

1. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
2. Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.
3. High variability in gastric emptying time due to its all or non-emptying process.
4. Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diametric size. Therefore patients should not be dosed with floating forms just before going to bed.

Floating tablets have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations [6]. Floating systems can be classified into two distinct categories, non-effervescent and effervescent systems. Bosentan is a dual endothelin receptor antagonist important in the treatment of pulmonary artery hypertension. Endothelin-1 is a neurohormone, the effects of which are mediated by binding to ETA and ETB receptors in the endothelium and vascular smooth muscle [7]. ET-1 concentrations are elevated in plasma and lung tissue of patients with pulmonary arterial hypertension, suggesting a pathogenic role for ET-1 in this disease.

2. Materials and Methods

Bosentan was the gift sample by Chandra labs, hyd, HPMC, Guar gum, Carbopol, Polyvinylpyrrolidine & talc (Gifted by Myl Chem Mumbai), Microcrystalline cellulose, Magnesium stearate & sodium bicarbonate (S.D Fine chem. LTD Mumbai) and all other chemicals & Solvents used were of analytical grade.

Methodology:

Drug -Excipient Compatibility Study:

Infrared spectroscopy is a useful analytical technique utilized to check the chemical interaction between the drug and excipients used in the formulation.1-2 mg of solid fine powder of drug and 200-300 mg of dry powder of KBr (IR grade) were taken in a mortar and mixed well with the help of a spatula. Spectrum measurement was carried out using KBr disk method in the wavelength region of 4000-400cm^{-1} by FTIR spectrophotometer [8]. The IR spectrum of the physical mixture was compared with that of the pure drug to check any possible drug-excipient interaction.

Formulation of bosentan gastroretentive floating tablets

The Bosentan floating tablet were prepared by direct compression method. Accuratly weigh the polymers Micro crystalline cellulose, Hydroxy propyl methyl cellulose, Ethyl cellulose, PVPK30 and different polymers were weighed and sifted through 40 mesh according to the formulation table. To the above blend Bosentan was added and sifted through 18 mesh. The sifted materials were mixed for 10min. Magnesium Stearate and talc was weighed and sifted through 40 mesh. To the above mixture lubricated blend was added and mixed properly. Then the blend was compressed using 168mm oval punch [9].

Evaluation of Precompression Blend Flow Properties:

Angle of Repose:

The flow property was determined by measuring the Angle of Repose. In order to determine the flow property, the Angle of Repose was determined. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal [10].

Angle of repose= $\tan^{-1}$ (h/r)

Where,

h = height of a pile (2 cm)

r = radius of pile base.

Bulk density:

Bulk density is ratio of given mass of powder and its bulk volume. Bulk density was determined by measuring the volume of known mass of powder sample that has been passed through the screen in to graduated cylinder or through volume measuring apparatus in to cup [11].

Bulk density = M / V_0

Where M= mass of the powder;

V_0=bulk volume of the powder.

Tapped density:

A known quantity of powder was transferred to a graduated cylinder and volume V_0 was noted. The cylinder fixed to a density determination apparatus, tapped for 500 times then reading was observed. The density is achieved by mechanically tapped by a measuring cylinder containing the powder sample. After observing the initial volume the cylinder is mechanically tapped and volume reading were taken until little further volume changes is observed [12].

Tap density = M / Vr

Where M = mass of the powder,

Vr = final tapping volume of the powder.

Compressibility index and Hausner ratio:

The compressibility index and hausner ratio may be calculated using measured values of bulk density and tapped density as follows:

Compressibility index = 100 × tapped density / bulk density

Hausner ratio = tapped density / bulk density

Flow properties and corresponding Angle of repose, Compressibility index and Hausner ratio:

Evaluation of tablets:

There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets [13]. These include the diameter, size, shape, thickness, weight, hardness, Friability and *in vitro* dissolution characters.

Hardness:

Hardness of the tablet was determined by using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force [14].

Thickness:

Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet is measured by Vernier Callipers scale [15].

Friability: Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping [16]. It is usually measured by the use of the Roche friabilator.

The percentage friability was determined by the formula:

% friability = $(W_1-W_2) / W_1 \times 100$

W_1 = Weight of tablets before test

W_2 = Weight of tablets after test

***In-vitro* Buoyancy studies:**

The *In-vitro* buoyancy was determined by floating lag time, and total floating time. The tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time and the duration of the time the tablet constantly floats on the dissolution medium was noted as the Total Floating Time respectively [17].

***In-vitro* Dissolution Studies of Bosentan floating tablet:**

In vitro drug release studies were carried out using USP XXIV dissolution apparatus type II, with 900ml of dissolution medium maintained at 37±1°C for 8 hr, at 50 rpm, 0.1 N HCl (pH 1.2) was used as a dissolution medium. 5ml of sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug free dissolution fluid [18]. The samples withdrawn were filtered through 0.45µ membrane filter, and drug release in each sample was analyzed after suitable dilution by UV/Vis Spectrophotometer at 269nm.

Release order Kinetics:

The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in the case of matrix systems [19]. As a model-dependent approach, the dissolution data was fitted to four popular release models such as zero-order, first-order, diffusion and Peppa's-Korsemeyer equations, which have been described in the literature. The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from the matrix systems was studied by using Higuchi equation and Peppa's- Korsemeyer equation.

Zero Order Release Kinetics:

It defines a linear relationship between the fractions of drug released versus time.

$$Q = k_o t$$

Where, Q is the fraction of drug released at time t and k_o is the zero order release rate constant.

First Order Release Kinetics:

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that drug release from most of the slow release tablets could be described adequately by apparent first-order kinetics. The equation that describes first order kinetics is

$$\ln (1-Q) = - K_1 t$$

Where, Q is the fraction of drug released at time t and k_1 is the first order release rate constant.

Higuchi equation: It defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time.

$$Q=K_2 t^{½}$$

Where, K2 is the release rate constant.

Power Law:

In order to define a model, which would represent a better fit for the formulation, dissolution data was further analyzed by Peppa's and Korsemeyer equation (Power Law).

$$M_t/M_\alpha = K.t^n$$

Where, M_t is the amount of drug released at time t and M_α is the amount released at time α, thus the M_t/M_α is the fraction of drug released at time t, k is the kinetic constant and n is the diffusion exponent. To characterize the mechanism for both solvent penetration and drug release n can be used as abstracted in Table. A plot between log of M_t/M_α against log of time will be linear if the release obeys

Peppa's and Korsemeyer equation and the slope of this plot represents "n" value.

3. Results and Discussion

Drug and excipient compatibility study:

Drug and excipients compatibility was studied by using FTIR studies. FTIR graphs for present research work were attached below. From below figures it was concluded that there was no change in the position and areas of peaks presented in pure drug compared to the final best formulation. So there was no incompatibility among these ingredients as shown in Figures 2 & 3.

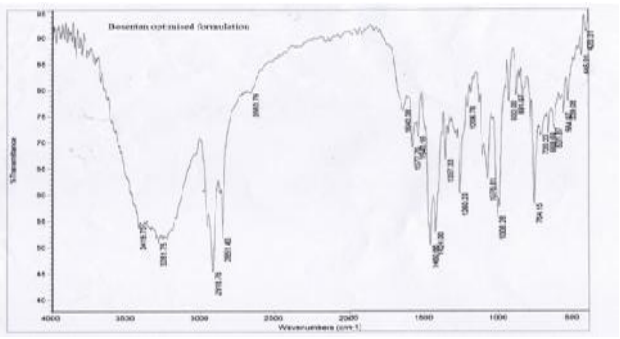

Figure 3: FTIR of F7 Optimized Formulation

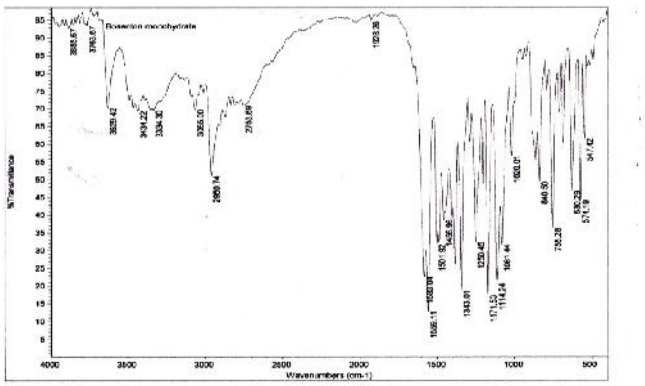

Figure 2: FTIR of bosentan Pure Drug

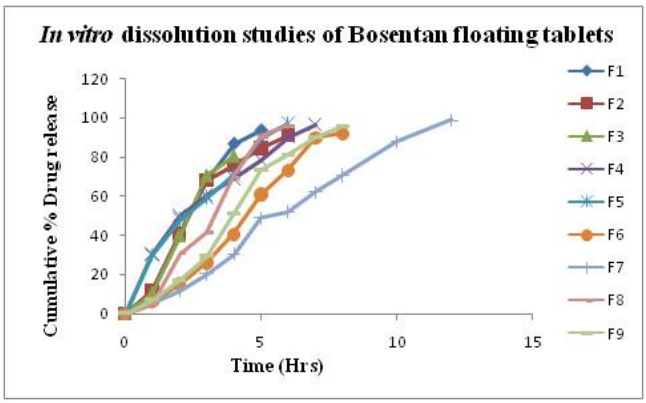

Figure 4: *In-vitro* dissolution studies of Bosentan floating tablets

Table 1: Composition *of* Bosentan floating tablets (F1 to F9)

Ingredients (mg)	**F_1**	**F_2**	**F_3**	**F_4**	**F5**	**F6**	**F7**	**F8**	**F9**
Bosentan	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5
HPMC (K4M) (%)	20	--	--	--	20	--	--	25	25
Guar gum (%)	--	20	--	20	--	25	25	--	--
Carbopol (%)	--	--	20	--	--	--	--	--	
Ethyl Cellulose (%)	--	--	--	5	5	5	10	5	10
Polyvinylpyrrolidine K30 (%)	5	5	5	5	5	5	5	5	5
Sodium Bicarbonate (%)	15	15	15	15	15	15	20	15	15
MCC (%)	qs	qs	qs	qs	qs	qs	qs	qs	qs
Talc (%)	2	2	2	2	2	2	2	2	2
Magnesium stearate (%)	2	2	2	2	2	2	2	2	2
Total weight (mg)	400	400	400	400	400	400	400	400	400

Table 2: Evaluation of pre compression parameters for bosentan floating tablets

Formulation code	**Angle of Repose (θ)**	**Loose Bulk Density (g/cc)**	**Tapped Density (g/cc)**	**Compressibility (%)**	**Hausner's ratio**
F1	24.6	0.45	0.52	13.4	1.15
F2	26.9	0.44	0.52	15.3	1.18
F3	24.2	0.45	0.51	11.7	1.13
F4	29.5	0.44	0.50	12.0	1.13
F5	20.6	0.45	0.52	13.6	1.15
F6	22.6	0.43	0.50	14.0	1.16
F7	23.1	0.44	0.52	15.3	1.18
F8	22.1	0.45	0.50	12.23	1.11
F9	23.01	0.44	0.50	12.58	1.13

Table 3: Post compression parameters for bosentan floating tablets

Formulation code	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Buoyancy Lag time (min)	Total floating time(hrs)
F1	6.8	2.96	0.12	12	08
F2	6.4	2.80	0.15	09	08
F3	6.4	2.81	0.22	13	04
F4	7.1	3.01	0.17	10	10
F5	6.5	2.89	0.27	11	11
F6	7.2	3.01	0.25	08	>12
F7	7.1	3.05	0.12	05	>12
F8	7.0	3.05	0.14	09	>12
F9	6.9	2.85	0.01	08	>12

Table 4: Swelling index studies of Bosentan floating Tablets

Time (hr)	Swelling index ratio								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
2	32	35	42	46	50	55	41	54	55
4	46	48	50	51	58	60	59	64	68
6	52	55	58	65	67	72	68	79	79
8	64	78	58	74	78	84	94	99	92
10	79	102	58	102	84	96	110	105	112
12	94	124	58	110	96	118	124	109	125

Table 5: *In-vitro* dissolution studies of Bosentan floating Tablets

Time in hrs	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	11.6	11.6	10.6	30.6	29.7	6.3	5.7	5.0	7.2
2	40.7	40.7	39.8	49.9	48.2	15.4	11.9	30.6	17.1
3	68.2	68.2	70.3	60.2	59.3	26.1	20.2	41.4	29.2
4	86.6	76.1	80.3	69.1	70.8	40.6	30.5	69.7	50.8
5	93.5	84.5		78.2	89.6	61.1	48.9	90.2	73.7
6		91.1		90.1	97.2	73.1	52.2	96	81.22
7				96.3		89.92	62.1		90.26
8						92	70.8		95.9
10							88.1		
12							99		

Table 6: Kinetic values obtained from different plots of F7 formulation

Release kinetics	Zero	First	Higuchi	Peppas
X & Y Scale	**% CDR Vs T**	**Log % Remain Vs T**	**%CDR Vs √T**	**Log C Vs Log T**
Slope	12.11497006	-0.27299952	36.40076973	1.521500637
Intercept	9.877245509	2.309745761	-7.99271293	0.813494663
Correlation	0.977788357	-0.88251212	0.984252365	0.7855883
R 2	0.956070071	0.778827644	0.968752718	0.617148976

4. Conclusion

The floating tablet containing Bosentan were successfully prepared by direct compression method. The physiochemical evaluation results for the granules of all trials pass the official limits in angle of repose, compressibility index. The optimized formulation F7 contains the average thickness of 3.05mm, average hardness of 7.1 kg/cm^2, friability of 0.12%, the buoyancy studies of the bosentan floating tablets show 5 mints to 13 mints & the total floating time of tablets 8 to more than 12 hours. The swelling index of floating tablet 124 mins. The *In-vitro* dissolution studies of floaing tablets of best formulation F7 shows 99% Drug release bosentan floating tablets within 12 hours. The furture plan to study the Scale up studies of the optimized formulation. *In-vivo* studies, *In-vivo* and *In-vitro* correlation studies to known the bioavailability studies.

5. References

[1] Robinson Jr, Lee V.H.L, Controlled drug delivery: Fundamentals and Applications, 2nd ed. Marcel Dekker, New York: (1978) P.24-36.

[2] Vyas S.P, Khar R.K, and Controlled Drug Delivery: Concepts and Advances, 1st ed. Vallabh prakashan, New Delhi: (2002) P.345-376.

[3] Chein Y.W, Novel Drug Delivery Systems, 2nd ed.: Marcel Dekker; New York: (1992) P.4-56.
[4] Banker G.S, Rhodes C.T, Modern Pharmaceutics. 3rd ed. Marcel Dekker, New York: (1996) P.678-721.
[5] P.G.Yeole, Floating Drug Delivery System: Need and Development, Ind. J. Pharm. Sci., (2005): 67(3); 265-272.
[6] Srivastava AK, Wadhwa S, Ridhurkar D, Mishra B. Oral sustained delivery of atenolol from floating matrix tablets-formulation and *In vitro* evaluation. Drug Dev. Ind. Pharm 2005; 31:367-74.
[7] Dave BS, Amin AF, Patel MM. Gastro retentive Drug Delivery System of Ranitidine Hydrochloride: Formulation & *In-vitro* Evaluation. AAPS Pharm. Sci. Tech 2004; 5.
[8] Dalavi V.V. and Patel J. S. Gastro retentive drug delivery system of an antiretroviral agent/Int. J. Pharm Tech Res.2009, 1(4) Vol.1, No.4, pg 1678-1684,
[9] M. Sivabalan, T Punitha Vani, Phaneendhar Reddy, Vasudevaiah, Anup Jose and G Nigila. Formulation and evaluation of gastro retentive Glipizide floating tablets. Int. J. Compre. Pharmacy *(IJCP) 2011, 1 (03).*
[10] S. B. Bhise and N. H. Aloorkar. Formulation and *In-vitro* Evaluation of Floating Capsules of Theophylline. Indian. J. Pharm Sci. 2008 Mar-Apr; 70(2): 224–227.
[11] Patel Amit, Jha Sajal Kumar, Panchal Harishanker, Shukla Tarkeshwar and Shah Arpit Formulation development and evaluation of Famotidine floating tablet**.** Int. J. Pharm. Sci., Vol: 4, Issue 3, Sep– Octo 2010; Pg. 224.
[12] Chander Shekar .B, Shireesh Kiran .R, and Nagendra Babu .B Preparation and evaluation of gastro retentive floating tablets of Ketoconazole. Int.j. Pharma Res and develop. November - 2010 / Vol: 2 / Issue - 9 pg, 174-184.
[13] Pramod Patel Formulation and *In vitro* Evaluation of Floating Matrix Tablets of Ofloxacin .Asian J. Res. Pharm. Sci. 2011; Vol. 1: Issue 1, Pg 17-22.
[14] Thakkar VT, Shah PA, Soni TG, Parmar MY, Gohel MC, Gandhi TR. Fabrication and evaluation of levofloxacin hemihydrates floating tablets. Res Pharm Sci 2008; Vol: 3, pg: 1-8.
[15] Bomma R, Swamy Naidu RA, Yamsani MR, Veerabrahma K. Development and evaluation of gastro retentive norfloxacin tablets. Act. Pharma 2009; Vol: 59: pg: 211-21.
[16] Rahman Z, Mushir A, Khar RK. Design and evaluation of Bilayer floating tablets of captopril. Act. Pharm 2006; Vol: 56: pg: 49-57.
[17] Li S, Lin S, Daggy BP, Mirchandani, HL, Chien, TW. Effect of formulation variables on the floating properties of gastric floating drug delivery system. Drug Dev. Ind. Pharm 2002; Vol-28: pg: 783-93.
[18] V. Lakshmi Narasaiah, G.Saravanan, M. Raj Kumar, B.Kalyan Reddy, P.Srikanth, M.Santosh Kumar, S.Satyanand and A. Ashok. Formulation, Characterization and *In-vitro* evaluation of Sumatriptan Succinate floating tablets. JITPS - 2010, Vol.1 (5), pg.192-203
[19] ST Prajapati, LD Patel and DM Patel Studies on Formulation and *In-vitro* Evaluation of Floating Matrix Tablets of Domperidone. Indian. J Pharm Sci. 2009 Jan-Feb; Vol-71(1): pg: 19–23.