IJBPAS, September, 2024, 13(9): 4588-4597

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

FORMULATION AND EVALUATION OF FLOATING TABLETS OF BOSENTAN BY MELT GRANULATION TECHNIQUE

RAVALIKA J*, RAMIREDDY GV AND RAMA RAO N

Department of Pharmaceutics, Chalapathi Institute of Pharmaceutical Sciences, Chalapathi Nagar, LAM, Guntur-522034, Andhra Pradesh, India

***Corresponding Author: Jammalamadugu Ravalika: E Mail:** ravalikajammalamadugu@gmail.com

Received 18th July 2023; Revised 20th Sept. 2023; Accepted 10th Dec. 2023; Available online 1st Sept. 2024

https://doi.org/10.31032/IJBPAS/2024/13.9.8335

ABSTRACT

Aim and objective: The present investigation aimed to formulate controlled-release bosentan floating tablets by hot melt granulation technique.

Method: Different quantities of xanthan gum and ethyl cellulose were used in the melt granulation process to prepare the floating tablets.

Results and discussion: The formulations were subjected to pre-compression parameters like angle of repose, bulk density, tapped density, Hausner's ratio, Carr's index, and post-compression parameters like hardness, floating lag time, floating time, and dissolution. The Pharmacopoeia limits were achieved for all formulations. Drug release from tablets was tested in vitro for 24 hours in 0.1 N HCl (pH 1.2). F6 was discovered to be the best formulation out of all the formulations, exhibiting 93.55% in-vitro drug release over 24 hours with a lag time of 9 seconds. By increasing the concentrations of polymers the drug release was prolonged. Drug-excipient compatibility studies have shown that there was no interaction between drug and excipients. Accelerated stability studies revealed a high degree of consistency with the original formulation, indicating the stability of the formulations. By using Sprague Dawley rats, *in-vivo* studies were carried out and pharmacokinetic parameters were determined.

Conclusion: From the results, conclude that the prepared bosentan floating tablets were able to prolong drug release, increased bioavailability, and have maximum therapeutic efficacy.

Keywords: Gastro-retentive drug delivery system, Bosentan, carnauba wax, xanthan gum, floating tablets, pH, *In vitro*

1. INTRODUCTION:

GRDDS is a novel drug delivery system that promotes site-specific release for local or systemic effects in the upper GIT by extending the gastric residence time **[1]**. It can float on the contents of the stomach and release the drug in a controlled manner for prolonged periods **[2]**. Over the past few decades, a variety of gastro-retentive drug delivery techniques have been created, such as high density or sink systems, low density, mucoadhesive, unfoldable, extendable, or swelling systems **[3]**.

Pulmonary arterial hypertension (PAH) is a persistent rise in mean pulmonary artery pressure of more than 25 mmHg at rest or more than 30 mmHg during activity. Women are more prone to PAH than men, and patients of all ages can be affected. It is a condition that is marked by syncope, tiredness, dyspnoea, and chest pain **[4]**.

The first Endothelin receptor antagonist (ERA) to successfully treat PAH is Bosentan, which is a dual-action sulfonamide-based endothelin receptor antagonist **[5]**. Endothelin-1 (ET-1) is a potent vasoconstrictor (a neurohormone) that mediates cell proliferation, fibrosis, and inflammation **[6]**. Drug absorption is quick and thorough following oral administration **[7]**. With a terminal half-life of around 5 hours, it is rapidly distributed, extensively bound to albumin, and removed. Insignificant amounts of medication are excreted unaltered in urine and feces **[8]**.

2. MATERIALS AND METHODS:

2.1 Materials:

Bosentan (drug) was obtained as a gift sample from Aurobindo Pharma Pvt. Ltd, Hyderabad. Carnauba wax and xanthan gum was obtained from BRM Chemicals, Delhi. Ethyl cellulose was obtained from LOBA CHEMIE PVT.LTD. All the other excipients used were of a standard analytical grade.

2.2 Method:

The melt granulation method was used to prepare the tablets. At 80 to 86°C, carnauba wax was melted. The molten wax was continuously stirred and bosentan, xanthan gum, ethyl cellulose, and sodium bicarbonate were gradually added. To obtain granules, this mixture was subsequently sieved via sieve no. 10. The mixture was given time to cool. Talc, lactose, and magnesium stearate were added to the dried granules. For the powder to flow uniformly, it was once again sieved. Utilizing a 9mm punch, the tablets were punched by 8 Station Rotary Tablet compression machine **[9]** (Cadmach).

Table 1: Composition of floating tablets of bosentan

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Bosentan	125	125	125	125	125	125	125	125	125
Carnauba wax	30	30	30	30	30	30	30	30	30
Xanthan gum	10	12	14	16	18	20	22	24	26
Ethyl cellulose	5	5	5	10	10	10	15	15	15
Sodium bicarbonate	55	55	55	55	55	55	55	55	55
Magnesium stearate	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2
Lactose	72	70	68	61	59	57	50	48	46
Total	300	300	300	300	300	300	300	300	300

3. EVALUATION TESTS:

3.1 Precompression parameters:

3.1.1 Angle of repose:

The angle of repose was determined by the funnel method. The granules were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2 cm above the hard surface. The granules were poured till the time when the upper tip of the pile surface touched the lower tip of the funnel **[10]**. The θ is calculated by the equation:

Tan θ = h/r

Where θ → Angle of repose

Tapped density = weight of the powder / tapped volume

3.1.4 Hausner's ratio:

Hausner found that this ratio was related to interparticle friction and, as such, could be used to predict powder flow properties. The equation for Hausner's ratio is as follows:

Hausner's ratio = Tapped density/bulk density [11]

3.1.5 Carr's index:

The flow ability of powder may be evaluated by comparing bulk density and tapped density of powder and the rate at which it packs down. It is also known as the compressibility index **[12]**. The percentage of the compressibility index was calculated by the following equation:

CI = (Tapped density – Bulk density) / Tapped density * 100

3.2 Post-compression studies:

3.2.1 Hardness:

Hardness indicates the ability of a tablet to withstand mechanical strength while handling. Tablet hardness was measured by using a Monsanto hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

3.2.2 Thickness:

The thickness of the tablet was determined randomly by selecting three tablets from each formulation using vernier calipers which were expressed in mm. The extent of deviation in the tablet formulation should not exceed the limit of ± 5% of their determined values **[13]**.

3.2.3 Friability:

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined by using the Roche Friabilator. Ten tablets were initially weighed (initial wt.) and transferred into a friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. Then, the tablets were dedusted and reweighed (final wt.). Friability was calculated using the following equation:

Friability (%) = Initial weight – Final weight / Initial weight * 100

3.2.4 Weight variation test:

The tablets were selected randomly from each formulation and weighed individually to check for weight variation. To study weight variation, 10 tablets of each formulation were weighed using an electronic balance and the average weight was calculated which was compared with the individual weight of the tablet. Any two tablet's deviation should not exceed the average weight **[14]**.

3.2.5 Lag time:

The floating tablets were put in a 0.1 N HCl-containing 100 mL beaker (37°C ± 1°C). The period taken to lift the tablet to the medium's surface is referred to as floating lag time or lag time for buoyancy.

3.2.6 Floating time:

The period during which the tablets have stayed continuously on the surface of the medium, on the other hand, is referred to as overall floating time or total buoyancy time **[15]**.

3.2.7 *In vitro* dissolution study:

Using the USP type-II dissolution equipment, the *in-vitro* release profile of bosentan from the created formulations was studied. The dissolution medium was 900 ml of 0.1 N HCl (^{pH} 1.2) at 37±0.5°C, and the paddle rotation speed was maintained at 50 rpm. 5 ml samples were collected from the dissolution apparatus hourly and replaced with new dissolution media. The absorbance was measured using a double-beam UV spectrophotometer at 242 nm **[16]**.

3.3 Stability studies:

As per the harmony of guiding principles as given by the International Conference on Harmonization (ICH) for Zone -IV, the study was accomplished. The prepared tablets(F6) were kept in an aluminum pack having an inner coat of polyethylene. The aluminum pack was then properly sealed. The pack was then kept inside the humidity chamber maintained at 35±2°C or 60±5% RH **[17]** for long-term conditions and 40±2°C or 75±5% RH under accelerated conditions for at least 6 months. The product is considered to be stable where there was no significant change in the stability studies **[18]**. The samples were examined for *in-*

vitro dissolution studies, hardness, and floating time.

3.4 *In vivo* studies:

Animal studies were performed according to the guidelines provided by the Committee for the purpose of control and supervision of experiments on animals (CPCSEA).

Sprague Dawley rats (200-250 g) of both genders were housed in a room under controlled conditions of temperature (22 ± 2˚C) and diurnal lighting (12 h darkness and 12 h light). Pharmacokinetic studies were conducted in 2 groups. Reference formulation (Marketed formulation Bosentan 62.5) and test formulation (F6) were administered to rats (n = 6) at 50 mg/kg dose by oral gavage.

Following oral administration, the blood samples (250-300 µL) were obtained from the tail vein in heparinized tubes at various time points of 0.25, 0.5, 1, 2, 4, 5, 6, 10, and 24 h. Then the samples were centrifuged at room temperature for 5 min at 7000 rpm. The supernatants were collected using a micropipette. All plasma samples were analyzed **[19]**.

All the relevant pharmacokinetic parameters such as maximum plasma concentration (C_{max}), time at which C_{max} occurred (T_{max}), biological half-life ($t_{1/2}$), elimination rate constant (K_{el}), absorption rate constant (K_a), area under curve (AUC) and mean residence time (MRT) were calculated by non-compartmental analysis in each case using plasma-drug concentration data. The plasma concentration-time profile was used to determine the maximum plasma concentration (C_{max}) and the time to attain maximum plasma concentration (T_{max}).

4. RESULTS AND DISCUSSION:

4.1 Pre-compression parameters: (Table 2)

4.1.1 FT-IR studies: (Figure 1, 2)

4.2 Post-compression parameters: (Table 3)

4.2.1 *In vitro* dissolution studies:

Among all the formulations, F6 shows 93.55% drug release and was selected as the best-optimized formulation based on the drug release and pre-formulation studies. The drug was released for up to 24 hours and it was prepared by xanthan gum and ethyl cellulose (20 and 10 mg). The percentage of drug released from the formulations was due to an increase in the concentrations of xanthan gum and ethyl cellulose **(Figure 3)**.

4.3 Stability studies:

The stability studies were carried out on optimized F6 formulation. The product was placed at 35±2°C or 60±5% RH for long-term conditions and 40±2°C or 75±5% RH under accelerated conditions for at least 6 months. The product was considered to be stable as there was no significant change in the stability studies **(Table 4)**.

4.4 *In vivo* studies: (Table 5) (Figure 4)

Table 2: Pre-compression parameters (mean±s.d., n=3)

Formulation	Angle of repose (°)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's ratio	Carr's index
F1	33.79±0.14	0.55±0.11	0.59±0.25	1.07±1.23	6.77±1.12
F2	35.33±0.22	0.37±0.29	0.42±0.71	1.13±1.57	11.9±1.35
F3	34.62±0.34	0.52±0.44	0.59±0.37	1.13±1.38	11.86±1.22
F4	32.81±0.63	0.49±0.32	0.57±0.33	1.16±1.32	14.03±1.03
F5	33.31±0.25	0.45±0.18	0.51±0.44	1.13±1.22	11.76±1.2
F6	24.91±0.84	0.55±0.75	0.61±0.65	1.10±0.41	9.83±0.55
F7	34.72±0.33	0.41±0.52	0.44±0.27	1.1±0.023	9.09±1.91
F8	32.67±0.39	0.52±0.77	0.59±0.81	1.13±0.54	11.86±1.7
F9	24.44±0.15	0.42±0.84	0.47±0.17	1.11±0.19	10.63±1.1

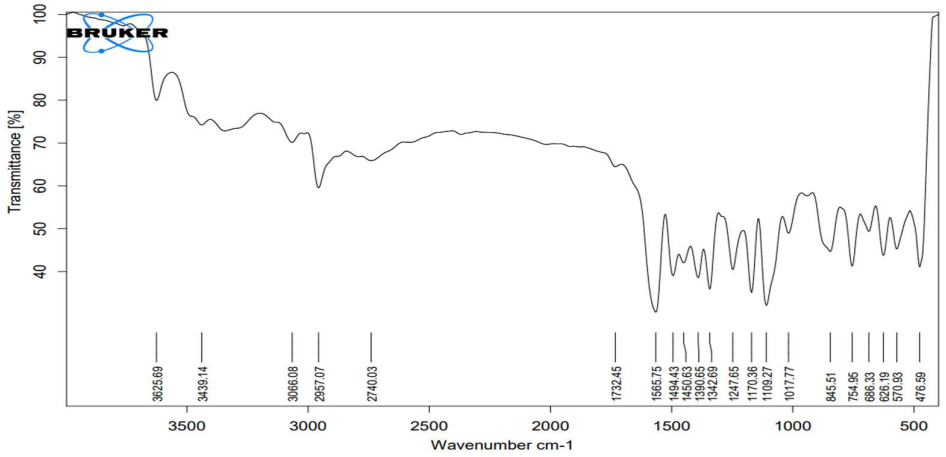

Figure 1: FT-IR spectrum of Bosentan

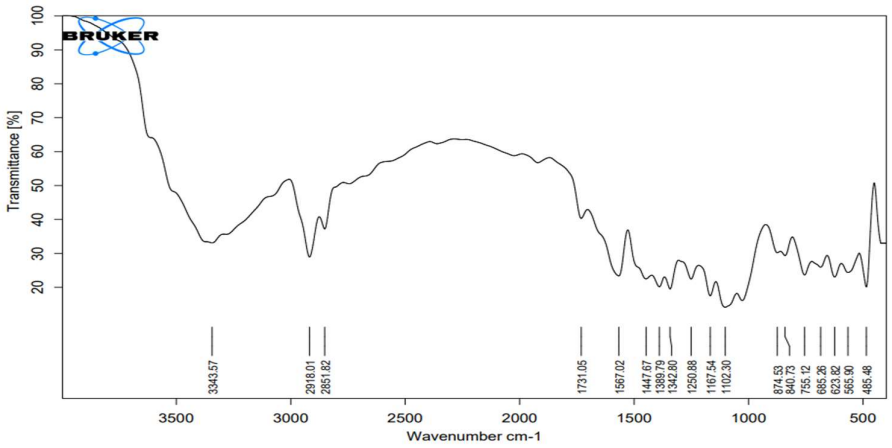

Figure 2: FT-IR spectrum of physical mixture

Table 3: Post-compression parameters of bosentan floating tablets (mean±s.d., n=3)

Formulation	Weight variation test	Thickness (mm)	Friability (%)	Hardness (kg/cm^2)	Floating lag time (sec)	Total floating time (hrs)
F1	287±0.11	2.98±0.11	1.11±0.01	3.5±0.15	5	15
F2	288±0.33	3±0.06	0.09±0.03	4±0.43	8	16
F3	299±0.98	2.97±0.06	0.08±0.02	4.2±0.32	15	17
F4	287±0.63	3.3±0.21	0.09±0.02	3.9±0.22	13	24
F5	288±0.15	2.98±0.32	0.07±0.01	4.4±011	10	24
F6	289±0.12	2.99±0.22	0.07±0.02	5.5±0.13	9	24
F7	288±0.97	2.89±0.55	1.07±0.03	3.6±0.57	11	>24
F8	289±0.11	3±0.27	0.06±0.01	5.1±0.45	12	>24
F9	287±0.42	2.98±0.16	0.03±0.02	5.3±0.12	15	>24

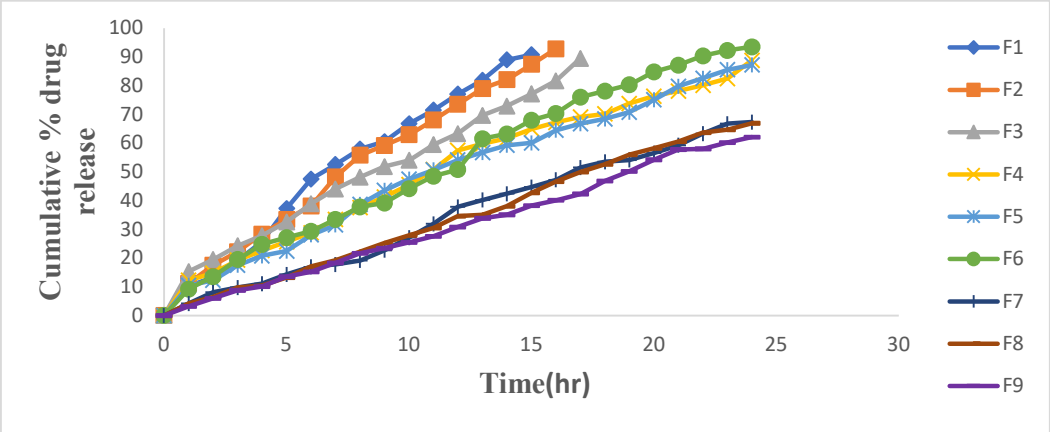

Figure 3: Bosentan release profile of F1 to F5 floating tablets (0.1N HCl)

Table 4: Stability studies of the optimized formulation F6 (mean±s.d., n=3)

Test	Storage conditions				
	35±2°C / 60±5% RH			40±2°C / 75±5% RH	
	Initial	3 months	6 months	3 months	6 months
In vitro dissolution studies	93.54±0.72	93.37±0.12	93.09±0.32	93.31±0.19	93.04±0.16
Hardness (kg/cm^2)	5.5±0.87	5.5±0.52	5.5±0.25	5.5±0.44	5.5±0.15
Floating time (h)	24	24	24	24	24

Table 5: *In vivo* pharmacokinetic parameters (mean ±s.d., n=3)

Parameter	Bosentan 62.5 mg	F6
C_{max} (ng/ml)	89.82±1.22	78.77±2.71
T_{max} (hr)	2.34±0.29	4.15±1.23
K_{el} (hr^{-1})	0.136±0.41	0.131±0.29
$t_{1/2}$ (hr)	4.91±0.55	4.96±0.99
K_a (hr^{-1})	2.03±0.37	1.91±0.71
AUC $_{(0-24)}$ (ng/hr/ml)	1355.27±1.43	5611.67±1.75
AUC $_{(0-\infty)}$ (ng/hr/ml)	3374.59±1.76	7993.28±2.78
MRT(hr)	4.2±0.44	18.77±0.23

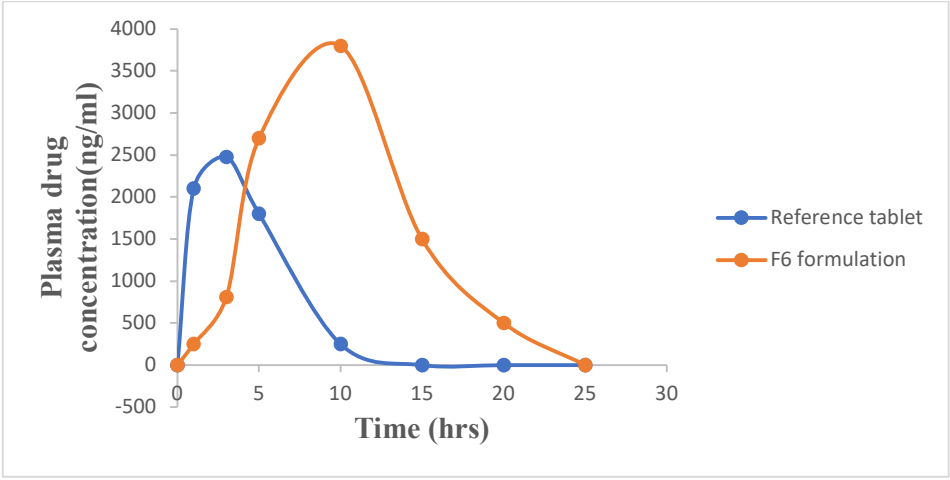

Figure 4: Plasma concentration-time profiles of F6 and reference tablet

The *in-vivo* data indicated that the F6 formulation exhibited a controlled release pattern compared to that of Bosentan 62.5 with enhanced bioavailability. Thus, the results indicated the applicability of bosentan floating tablets in the design of controlled-release drug delivery systems.

5.CONCLUSION:

The present investigation indicated that the applicability of xanthan gum and ethyl cellulose increases the drug release for a longer time. The optimized formulation showed 93.55% drug release for 24 hours with a floating lag time of 9 seconds. The major mechanism of drug release follows zero-order kinetics and non-fickian diffusion i.e., the polymer swelling and drug dissolution govern the drug release from the matrix. By increasing the concentrations of polymers the drug release was prolonged. Drug-excipient compatibility studies showed that there was no interaction between drug and excipients. The floating tablets showed a diffusion mechanism rather than an erosion mechanism. Accelerated stability studies revealed a high degree of consistency with the original formulation, indicating the stability of the formulations. By using Sprague Dawley rats, *in-vivo* studies were carried out and pharmacokinetic parameters were determined.

6. Acknowledgement:

It is our privilege to acknowledge my deep indebtedness to Dr. Rama Rao Nadendla, Principal of Chalapathi Institute of Pharmaceutical Sciences for providing facilities and carrying out the experiment successfully. We would like to express my special gratitude and thanks to my advisor Dr. G.V. Ramireddy, Professor.

7. REFERENCES:

[1] Ashok Thulluru, Manthena Mohan Varma, Chitrali Mallikarjuna Setty, Pavan Kumar Chintamaneni, and Sriharshavardhan Samayamanthula. Effect of Sodium Alginate in Combination with HPMC K 100 M in Extending the Release of Metoprolol Succinate from its Gastro-Retentive Floating Tablets. Indian Journal of Pharmaceutical Education and Research | Vol 49 | Issue 4 | Oct-Dec, 2015.

[2] Dalavi V. V and Patil J. S. Statistical Optimization and Development of Gastro Retentive System 2 of an Antiretroviral Drug using a 3 Factorial Design. Indian J.Pharm. Educ. Res. 44(3), Jul-Sep, 2010.

[3] Poornima, Sneh Priya. Gastroretentive Floating Tablets Enclosing Nanosponge Loaded with Lafutidine for Gastric Ulcer: Formulation and Evaluation. Indian Journal of Pharmaceutical Education

and Research | Vol 55 | Issue 1 [Suppl] | Jan-Mar, 202.

[4] Eli Gabbay, John Fraser, Keith McNeil. Review on Bosentan in the management of pulmonary arterial hypertension. Vascular Health and Risk Management 2007:3(6) 887-900.

[5] Muzaffar Iqbal, Essam Ezzeldin, Naser L Rezk, Amal A Bajrai & Khalid A Al-Rashood. A validated UPLC–MS/MS method for flibanserin in plasma and its pharmacokinetic interaction with bosentan in rats. Doi:-10.4155/bio-2018-0065.

[6] Lewis J Rubin, Sébastein Roux. Bosentan: a dual endothelin receptor antagonist. Expert Opin. Investig. Drugs (2002) 11(7):991-1002.

[7] Bhupendra Prajapati , Umang Varia. Bosentan-loaded Microemulsion: A Novel Formulation and Evaluation of their In vitro and In vivo Characteristic. Int. J. Pharm. Sci. Drug Res. September-October, 2020, Vol 12, Issue 5, 464-472.

[8] Mamatha Jirra, Dr. K. V. Ratnamala. Formulation and Evaluation of Gastroretentive Bosentan Monohydrate Tablets Using Raft Technology. Ijppr. Human, 2017; Vol. 11 (1): 142-159.

[9] Vidya P. Sabaleand Gunjan G. Gadge. Factorial design approach to fabricate and optimize floating tablets based on combination of natural polymer and rice bran wax. Beni-Suef Univ J Basic Appl Sci (2022) 11:5. Doi:-https://doi.org/10.1186/s43088-021-00186-9.

[10] Deepika K, Alla Narayana Rao, A. Bhavana, N.V. Ramana, Kalyani G. Formulation and evaluation of gastro retentive drug delivery of Eprosartan mesylate using the raft-forming approach. PHARMANEST - An International Journal of Advances in Pharmaceutical Sciences Volume 5|Issue 6| November-December 2014.

[11] Rashmitha V, Madhusudan Rao Y, Pavani S. Formulation and evaluation of Fenoverine floating tablets. Asian J Pharm Clin Res, Vol 14, Issue 4, 2021, 175-180.

[12] Nagaraju D., Taher Patelb and Dr. N Siva Subramanian. Formulation and development of in-vitro evaluation of gastro retentive floating tablets of quinapril. World Journal of Pharmaceutical Research. Vol 7, Issue 3, 2018.

[13] Susma Acharya, Jitendra Pandey, Hari Prasad Joshi, Gyanu Parajuli,

Narayani Poudel, Srijana Poudel, Shila Gurung. Formulation and evaluation of gastro retentive floating tablet of Amlodipine besylate using natural organic polymers. Int J App Pharm, Vol 14, Issue 4, 2022, 227-234.

[14] J. Padmavathy, D. Saravanan, D. Rajesh. Formulation and evaluation of ofloxacin floating tablets using HPMC. Int J Pharm Sci, Vol 3, Issue 1, 2011. Pg no.- 170-173.

[15] Purushottam Shridhar Gangane, Tejas Pachpute, Debarshi Kar Mahapatra, Nilesh Manoharrao Mahajan. HPMC Polymers and Xanthan Gum Assisted Development and Characterization of Stavudine Extended Release Floating Tablets. Indian Journal of Pharmaceutical Education and Research | Vol 55 | Issue 3(Suppl) | Jul-Sep, 2021.

[16] Sonam Sanjayrao Kunjekar, Dilesh Jagdish Singhavi, Tejaswini Balkrishna Parshuramkar, Shagufta Khan. Dual-pulse Release System of Atenolol: Preparation and in-vitro Characterization. Indian Journal of Pharmaceutical Education and Research | Vol 56 | Issue 4 | Oct-Dec, 2022.

[17] Yashpal Singh Chauhan, Udichi Kataria, Ashok Dashora. Formulation and evaluation of floating tablet for indomethacin. Journal of Drug Delivery & Therapeutics. 2018; 8(4):338-345.

[18] P.Madhuri, K.V Ratnamala. Formulation and Evaluation of Bosentan Monohydrate Sustained Release Tablets Using Thermal Sintering Technique. Am. J. PharmTech Res. 2020; 10(6).

[19] Duygu Yilmaz Usta, Burcu Timur, Zeynep Safak Teksin. Formulation development, optimization by Box-Behnken design, characterization, in vitro, ex-vivo, and in vivo evaluation of bosentan-loaded self-nano emulsifying drug delivery system: A novel alternative dosage form for pulmonary arterial hypertension treatment. European Journal of Pharmaceutical Sciences 174 (2022) 106159.