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FORMULATION AND *IN-VITRO* EVALUATION OF BOSENTAN MONOHYDRATE GASTRORETENTIVE TABLETS FOR TREATMENT OF PULMONARY ARTERY HYPERTENSION

***[1]Dr. Putta Rajesh Kumar, [2] Shazina Maher, [3]Syed Abdul Rehman, [4]Dr. Avanapu Srinivasa Rao**

[1,2]Department of Pharmaceutics, [3,4]Department of Pharmacy Practice
Bhaskar Pharmacy College, Yenkapally, Hyderabad, Telangana, India.

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***Corresponding Author**
Dr. Putta Rajesh Kumar
Department of Pharmaceutics Bhaskar Pharmacy College, Yenkapally, Hyderabad, Telangana, India.

ABSTRACT

Aim: Bosentan monohydrate is an endothelin receptor antagonist which is used for the treatment of pulmonary artery hypertension. Bosentan monohydrate gastro retentive tablets were formulated in the present research by using various polymers, sodium bicarbonate as gas generating agent by wet granulation technique. Absorption maximum of Bosentan monohydrate was determined; analytical method was developed and calibration curve was constructed. **Methods:** The formulation blend was subjected to various flow properties, post compression and floating parameter studies. *In vitro* dissolution studies were conducted and release data was subjected to kinetic analysis. **Results:** Calibration curve showed high degree of linearity which represents the sensitivity and accuracy of developed UV analytical method. Pre compression parameters revealed that all results were within the ideal limits indicated the suitable flow properties of the powder blend. All Bosentan monohydrate gastro retentive tablets indicated uniform post compression parameters like weight uniformity, thickness, hardness, friability. Floating parameters indicated the floating ability and prolonged floating duration for gastro retentive delivery of Bosentan monohydrate. Drug content studies revealed all formulations showed uniform drug content. *In vitro* studies revealed that Bosentan monohydrate release is sustained and prolonged for 8 – 12 hr which ensures selective drug absorption from stomach and patience compliance. **Conclusion:** Formulation S6 was identified as optimised formulation with respect to its ideal pre and post compression properties, floating parameters and *in vitro* drug release sustained for prolonged period. Release kinetic analysis of optimized formulation revealed that the S6 formulation followed zero order kinetics of drug release.

KEYWORDS: Floating matrix, Bosentan monohydrate, polymers, Effervescent agents, drug release studies.

INTRODUCTION

Oral route has been the commonly adopted and the most convenient route for the drug administration. Although tremendous advances have been seen in oral controlled drug delivery system in the last two decades, this system has been of limited success in the case of drugs with a poor absorption window throughout the GIT (Gastro Intestinal Tract). In the development of oral controlled drug delivery system, one of the main challenges is to modify the GI transit time.[1]

Gastroretention is essential for drugs that are absorbed from the stomach, they are also useful for local as well as sustained drug delivery for certain conditions, like H. pylori infection which is the cause of peptic ulcers. This dosage form improves bioavailability, therapeutic efficacy and may even also allow a possible reduction in the dose because of steady therapeutic levels of drug.[2,3] Gastroretensive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.[4,5]

Types of Gastroretentive Dosage Forms:[6-10] Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. Non-effervescent systems swell unrestrained via imbibition of gastric fluid in stomach. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Colloidal gel barrier system Microporous compartment system Alginate beads. Gas-generating (Effervescent) systems prepared with swellable polymers such as methocel, polysaccharides (e.g., chitosan), effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid). Expandable gastroretentive dosage forms (GRDFs). Bioadhesive drug delivery systems (BDDS). High-density systems with barium sulphate and titanium dioxide (table 1).

Mechanism of Floating Systems[11] Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents (Fig.1a), the drug is released slowly at the desired rate from the system.

However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side (Fig.1b). F = F buoyancy - F gravity; F= (Df - Ds) gv; Where, F = total vertical force, Df = fluid density, Ds = object density, v = volume, g = acceleration due to gravity. Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability (figure 1).

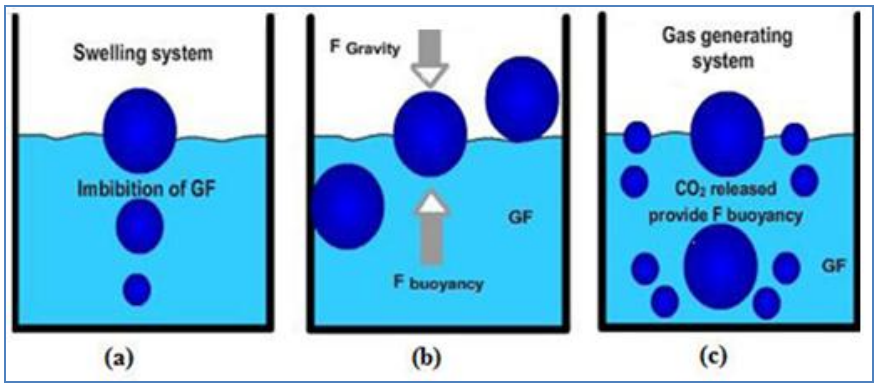

Fig. 1: Mechanism of floating drug delivery systems in Gastric fluid.

Table 1: Commercially available marketed Floating drug delivery Formulations.[12,13]

Name	Type and Drug	Remarks
MadoparHBS®(PropalHBS)	Floating capsule, Levodopa and Benserazide	Floating CR capsules
Valrelease®	Floating capsule, Diazepam	Floating Capsules
Topalkan®	Floating Antacid, aluminum and magnesium mixture	Effervescent floating liquid alginate preparation
Amalgate Float Coat®	Floating antacid Floating gel	Floating dosage form
Conviron	Ferrous sulphate	Colloidal gel forming FDDS
Cifran OD®	Ciprofloxacine (1 gm)	Gas generating floating form
Cytotech®	Misoprostol (100 mcg/200 mcg)	Bilayer floating capsule
Liquid Gaviscone®	Mixture of alginate	Suppress gastroesophageal reflux and alleviate

Bosentan monohydrate is a dual endothelin receptor antagonist important in the treatment of pulmonary artery hypertension (PAH). Mechanism of action: Endothelin-1 (ET-1) is a neurohormone, the impacts of which are intervened by official to ETA and ETB receptors in the endothelium and vascular smooth muscle. ET-1 fixations are raised in plasma and lung

tissue of patients with pneumonic blood vessel hypertension. Pharmacokinetics: Bioavailability is 50 % and Half-life 5 h. Bosentan is utilized to treat pneumonic blood vessel hypertension (PAH, hypertension in the vessels that convey blood to the lungs) in grown-ups and youngsters.[14, 15]

MATERIALS AND METHODS

Bosentan monohydrate was procured from Hetero labs, Hyderabad; PVPk30, HPMC, Sodium alginate, Guar gum, Xantham gum from S. D Fine chemicals, Mumbai, Sodium bicarbonate, Microcrystalline cellulose, Magnesium stearate, Talc obtained from AR Chemicals, Mumbai. All other chemicals used were of analytical grade.

Methodology

Preformulation studies[16]

Physical properties: The colour odour, taste of the drug was recorded using descriptive terminology. Solubility studies: Solubility study of Bosentan monohydrate was performed in various solvents Determination of melting point: Melting point of Bosentan monohydrate was determined by capillary method.

Analytical Method Development for Bosentan monohydrate[17,18]

Preparation of Buffer pH 1.2: 8.5ml of HCL dissolved in 1000ml of water. Preparation of standard solution of Bosentan monohydrate: 100 mg of drug was taken in a 100 ml volumetric flask. To that 1 ml of methanol was added and shaken well to dissolve the drug. The solution was made up to the mark with 0.1N HCl. From the above solution 1 ml is diluted to 10 ml with, 0.1N HCl solution to give 100 µg /ml concentration. From the above solution 1 ml is diluted to 10 ml with, 0.1N HCl solution to give 10 µg /ml was scanned for λ_{max} from 200-400 nm in UV/Visible spectrophotometer.

Preparation of Formulation:[23] Different tablet formulations were set up by wet granulation technique (table 2). The preparations are made out of polymers natural and synthetic polymers. All powders were gone through 100-work sieve. Alternate excipients and the polymer were blended consistently. Drug was added to the polymers and mixed for 20 min. Solution of PVP K30 added to the above blend for making dump mass. Dump mass was gone through sifter no. 40 and dried the granules for 2 hrs at 50^{o} c. The subsequent granules were blended with magnesium Stearate and powder in polyethylene bag for 10 min. The greased up granules were compacted utilizing 10mm punch (single punch tablet machine) in to

tablets. Pressure weight was balanced amid tableting of every equation to get the tablet hardness in the scope of 2.5 to 6 Kg/cm^3. The aggregate weight of tablet was kept at 200 mg.

Table 2: Formulation composition of Bosentan monohydrate gastro retentive tablets.

Ingredients (mg)	Formulations											
	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12
Bosentan onohydrate	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5
PVP K-307.5%	15	15	15	15	15	15	15	15	15	15	15	15
HPMCK15M 12.5,25%	25	-	-	-	-	50	-	-	-	-	25	-
HPMC K4M 12.5,25%	-	25	-	-	-	-	50	-	-	-	-	25
Sodium alginate 12.5,25%	-	-	25	-	-	-	-	50	-	-	-	-
Xantham gum 12.5,25%	-	-	-	25	-	-	-	-	50	-	25	-
Guar gum 12.5,25%	-	-	-	-	25	-	-	-	-	50	-	25
MCC 25%	50	50	50	50	50	50	50	50	50	50	50	50
Sodium bi carbonate 7.5%	15	15	15	15	15	15	15	15	15	15	15	15
Lactose 13.75,1.25%	27.5	27.5	27.5	27.5	27.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium stearate 1.5%	3	3	3	3	3	3	3	3	3	3	3	3
Talc 1%	2	2	2	2	2	2	2	2	2	2	2	2
Total wt 100%	200	200	200	200	200	200	200	200	200	200	200	200

Pre compression parameters (Flow property studies)[19-21]

Bulk Density:[19-21] Mass thickness is characterized as the mass of powder isolated by mass volume. Mass thickness = weight of test taken/volume noted.

Tapped density:[19-21] A precisely measured amount of the powder (W) was deliberately filled the graduated barrel and the volume (Vo) was estimated. Tapped thickness = weight of test taken/tapped volume.

Compressibility index (CI):[19-21] The CI was expressed in percentage calculated by CI= (V_i-V_t/V_i) x 100. This indicates the compression ability of the granular bed.

Hausner's ratio:[19-21] It is measured by the ratio of tapped density and bulk density.

Angle of repose:[19-21] The stream attributes are estimated by point of rest. Edge of rest is characterized as the most extreme point conceivable between the surface of a heap of the powder and the even plane. Tan Ø = h/r; Where; h = height of the pile, r = radius of pile base.

Drug-excipient compatibility studies:[22] The FTIR retention spectra of the Bosentan monohydrate sedate and with different excipients were taken in the extent of 4000-450 cm-1 using KBr plate system, 1-2 mg of the substance to be dissected was triturated with 300-400 mg, decided sum, of finely energized and dried potassium bromide.

Post compressional evaluation of tablets[24]

Physical Appearance:[24] The control of general appearance involves the measurement of size, shape, colour, presence or absence of odour, taste etc.

Thickness:[24] The thickness of the tablets was determined by using Vernier calipers. Five tablets were used, and average value was calculated.

Weight variation studies:[24] Weight variation was carried out to ensure that, each of tablets contains the proper amount of drug. The test was carried out by weighing the 20 tablets individually using analytical balance, then calculating the average weight, and comparing the individual tablet weights to the average. Percentage of weight variation = Individual weight-Average weight/Average weight x 100.

Hardness test:[24] This was performed using Monsanto hardness tester. The tablet was placed between two anvils; force applied to the anvils, and the crushing strength that just causes the tablet to break was recorded. The crushing strength test was performed on 20 tablets from each formulation.

Friability studies:[24] The friability was done by Roche Friabilator. Twenty medications have been at first weighed and moved into friabilator and operated at 25 rpm for four minutes for 100 upheavals. The tablets were taken out dedusted and weighed The rate friability was then determined by; % Friability = (W1-W2)/W1 X 100; W1 = Weight of tablets before test, W2 = Weight of tablets after test.

Drug content studies:[24] Ten tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in 0.1NHCl, the drug content was determined measuring the absorbance after suitable dilution using a Simadzu UV- Vis double beam spectrophotometer.

***In vitro* buoyancy studies:**[24] The *In vitro* buoyancy was determined by floating lag time method described by Dave B.S. The tablets were placed in 250ml beaker containing 0.1 N HCl. The floating lag time and Total Floating Time were measured for all formulations.

Drug release studies:[24] The drug release from the tablets was investigated in a USP-II (paddle), 900 ml of 0.1N HCl (50 rpm, 37°C). At predetermined time intervals, 5 ml samples were withdrawn and take 1ml sample and diluted to 10 ml and then analyzed in UV.

***In vitro* drug release kinetics:**[25, 26] The obtained dissolution data was fitted into various kinetic models to understand the pattern and mechanism of drug release from tablets. The models used were zero order, First order, Higuchi model and Koresmeyer Peppa's model.

Stability studies:[18, 27] Bosentan monohydrate floating tablets were tested at 40±2°c and 75% RH conditions for 3 months.

RESULTS AND DISCUSSION

Preformulation studies: Bosentan monohydrate was white solid powder. Bosentan monohydrate is freely soluble DMSO. Partially soluble in water. Sparingly soluble in acetone.

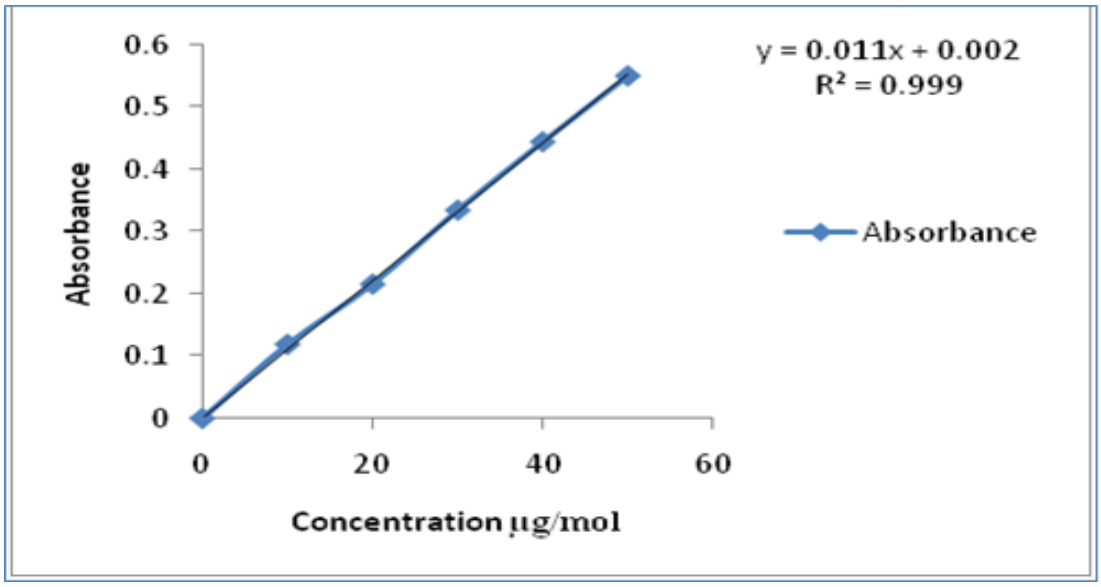

Fig. 2: Calibration curve of Bosentan monohydrate.

Drug –Excipient compatability studies.

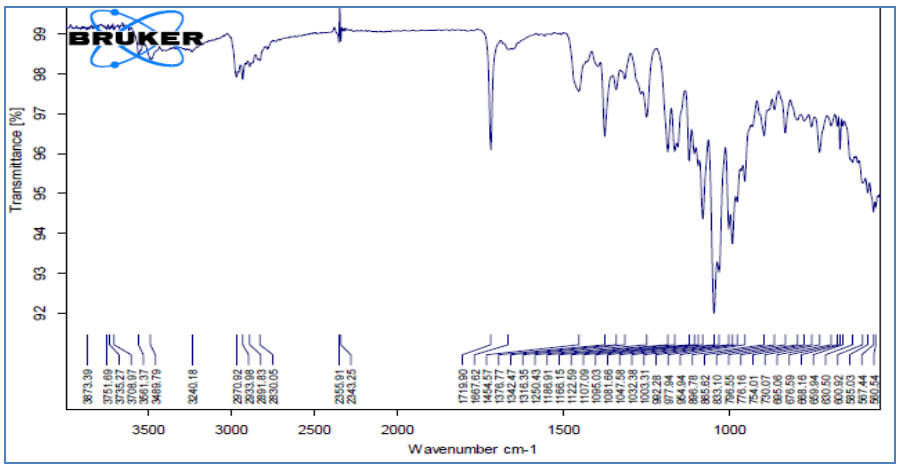

Fig. 3: FTIR studies of Pure drug Bosentan monohydrate.

Table 3: FTIR studies of Bosentan monohydrate.

S.No.	Characteristic Peaks	Frequency range (cm^{-1})	Frequency (cm^{-1})
1	OH stretching	3500-3000	3489.19
2	OH Bending	3000-2500	2933.98
3	C-H stretching	2500-2000	2355.91
4	C-N stretching	2000-1500	1667.62
5	C=O stretching	1500-1000	833.1

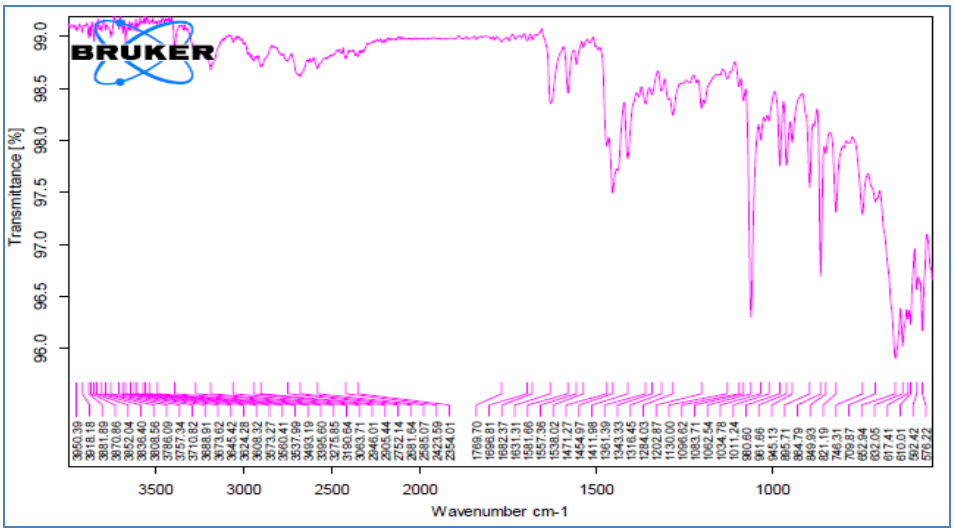

Fig. 4: FTIR studies of Optimized formulation.

Table 4: FTIR studies of Optimized formulation.

S.No.	Characteristic peaks	Frequencyrange (cm^{-1})	Frequency (cm^{-1})
1	OH stretching	3500-3000	3710.32
2	OH Bending	3000-2500	3537.12
3	C-H stretching	2500-2000	2946.01
4	C-N stretching	2000-1500	1538.66
5	C=O stretching	1500-1000	980.60

Table 5: Evaluation of pre compression parameters.

Formulation	Angle of repose (θ^{o})	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's index (%)	Hausner's ratio
S1	32	0.425±0.26	0.523±0.21	18.73±0.18	1.23±0.21
S2	29	0.432±0.19	0.542±0.24	20.29±0.20	1.25±0.20
S3	28	0.428±0.21	0.538±0.25	20.44±0.19	1.25±0.12
S4	30	0.425±0.19	0.524±0.27	18.89±0.23	1.23±0.14
S5	29	0.433±0.20	0.549±0.21	21.12±0.17	1.26±0.18
S6	30	0.441±0.26	0.568±0.15	22.35±0.23	1.28±0.19
S7	29	0.438±0.25	0.551±0.17	20.50±0.18	1.25±0.23
S8	28	0.440±0.15	0.555±0.20	20.72±0.17	1.26±0.19
S9	27	0.437±0.18	0.549±0.25	20.40±0.19	1.25±0.18
S10	31	0.436±0.17	0.548±0.22	20.43±0.21	1.25±0.20
S11	29	0.442±0.21	0.569±0.19	22.31±0.22	1.28±0.16
S12	30	0.436±0.15	0.546±0.18	20.14±0.18	1.25±0.15

Precompression parameters (Flow properties of granules): The results for angle of repose (θ) obtained was found to vary from 27-32. The Bulk and Tapped density of material blend ranged from 0.432-0.441gm/ml and 0.523-0.569 gm/ml respectively. Carr's index calculated showed to vary from 18.73-22.35% indicating that the blend has a good flow property, whereas Hausner's ratio analyzed is in 1.23-1.28 range representing a good flow properties.

Post compression parameters

Table 6: Evaluation of Post compression parameters.

Form. Code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)	Floating lag time (sec)
S1	200±0.22	3.22±0.19	3.98±0.18	0.23±0.23	97.16±0.18	95±0.19
S2	199±0.19	3.53±0.20	4.12±0.19	0.28±0.19	96.28±0.20	91±0.20
S3	198±0.20	3.30±0.17	4.09±0.23	0.24±0.25	95.88±0.21	98±0.21
S4	199±0.15	3.29±0.21	3.99±0.20	0.26±0.18	97.90±0.19	96±0.18
S5	197±0.23	3.32±0.23	4.11±0.15	0.25±0.23	96.85±0.23	92±0.21
S6	200±0.20	3.45±0.19	4.08±0.17	0.23±0.21	94.99±0.20	98±0.23
S7	197±0.19	3.49±0.14	4.18±0.19	0.27±0.24	97.20±0.21	93±0.22
S8	200±0.18	3.50±0.17	4.15±0.23	0.24±0.20	95.66±0.19	90±0.19
S9	199±0.22	3.48±0.18	4.16±0.20	0.25±0.24	94.80±0.20	89±0.23
S10	198±0.16	3.39±0.23	4.12±0.18	0.22±0.23	94.70±0.23	90±0.18
S11	200±0.19	3.40±0.21	4.11±0.24	0.28±0.25	97.56±0.19	91±0.21
S12	199±0.20	3.50±0.19	4.13±0.25	0.24±0.20	96.60±0.23	89±0.23

Evaluation of tablet: All the evaluated parameters result obtained from different formulations of tablet is shown in Table. Hardness of various tablets 3.98-4.16 were in range of kg/cm^2 enabling good mechanical strength. The thickness observed was 3.22-3.55 mm. The friability of tablet formulations was within the acceptable limits and ranged from 0.22-0.28%.Weight variation of various tablets were in range of 197-200mg and was within limits.

***In-vitro* drug release studies**

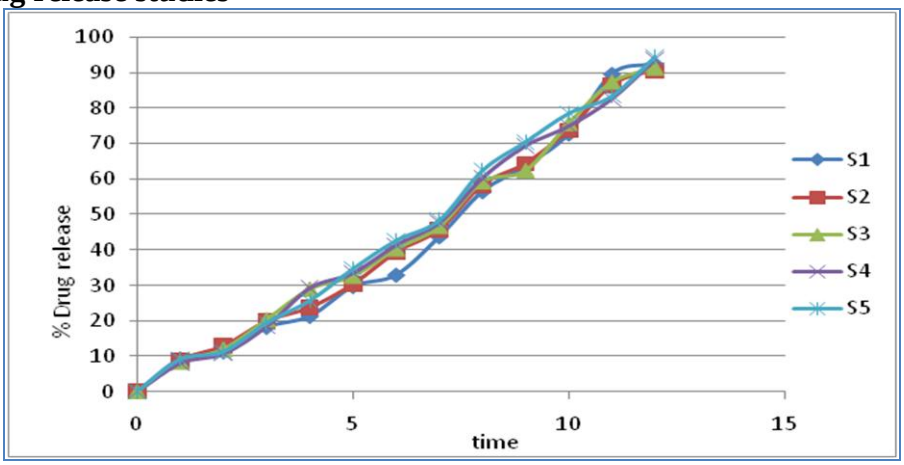

Fig. 5: *In vitro* Drug release studies of (S1-S5) Bosentan formulations.

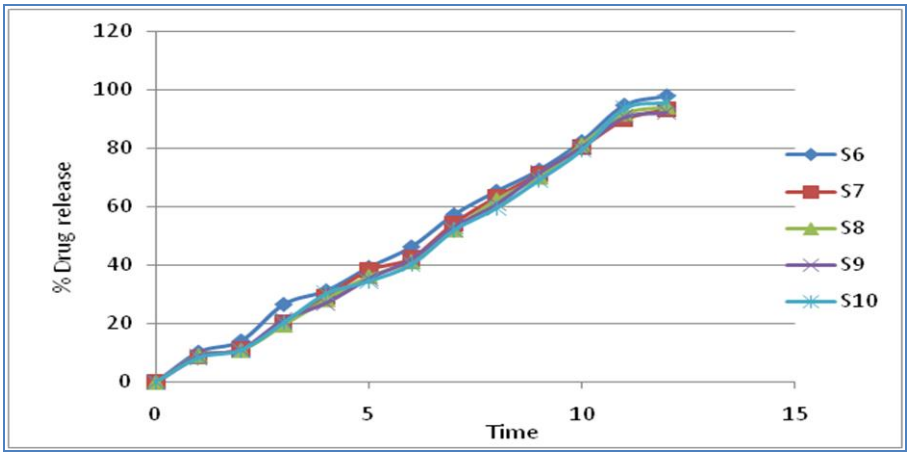

Fig. 6: *In vitro* Drug release studies of (S6-S10) Bosentan formulations.

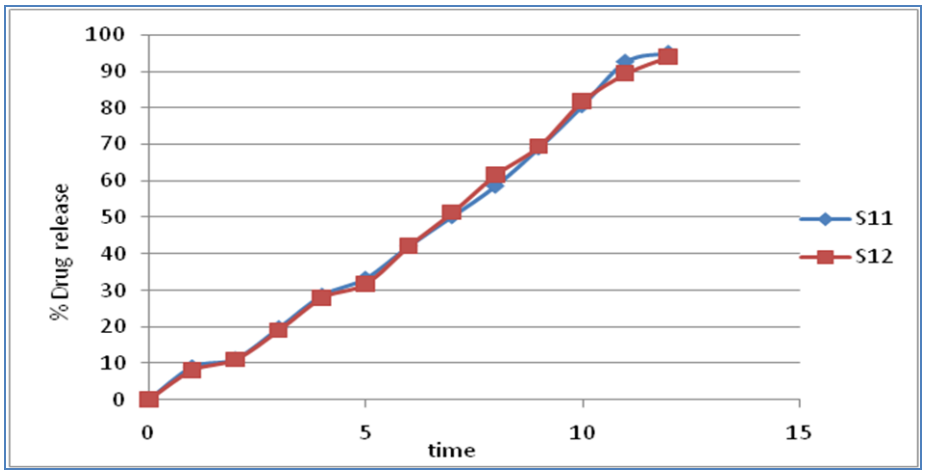

Fig. 7: *In vitro* Drug release studies of (S11-S12) Bosentan formulations.

The drug release from the tablets were explained by the using mathematical model equations such as zero order, first order, Higuchi`s Korsmeyer Peppa's methods. Based on the regression values it was concluded that the optimized formulation S6, followed first order release where the regression value was found to be 0.953. It was indicated that the optimized formulation S6, followed zero order release where the regression value was found to be 0.990. It was also found that the drug was released by diffusion as the regression in Higuchi's plot was 0.586.

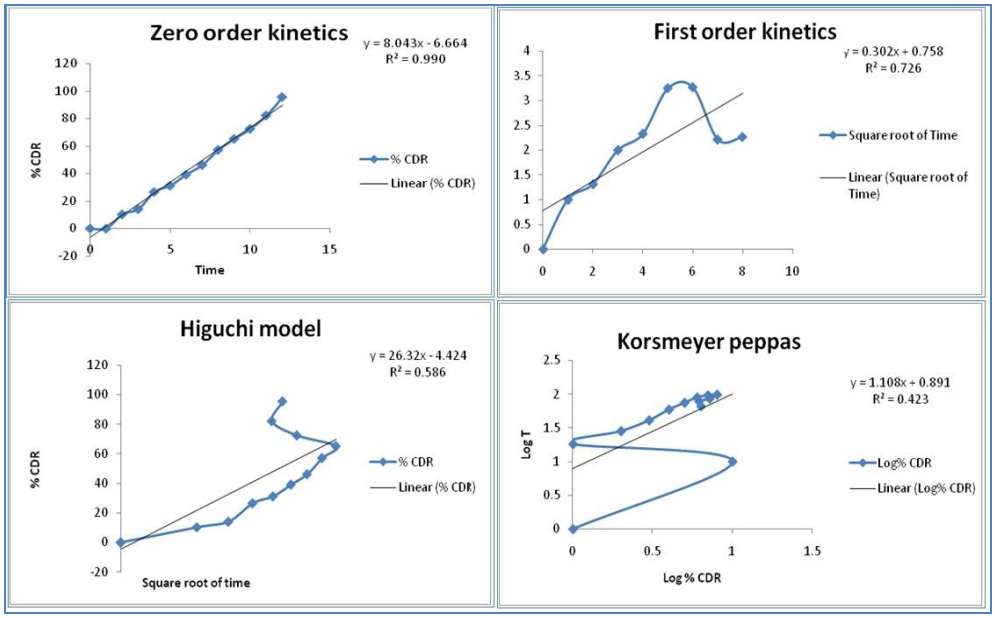

Fig. 8: Drug release kinetics study for the optimized formulation (S6).

Stability studies

Table 7: Stability studies of optimized formulation S6 at 40 ± 2 ^{0}C and 75 ± 5% RH.

S.No	Formulation Code	Initial	1st Month	2nd Month	3rd Month
1	S6	97.86±0.89	97.83±0.78	97.82±0.82	97.79±0.79
2	S6	97.86±0.89	97.81±0.69	97.79±0.85	97.67±0.83
3	S6	97.86±0.89	97.80±0.47	97.68±0.88	97.65±0.80

Optimized formulations S6 was selected for accelerated stability studies as per ICH guidelines. The tablets were observed for a period of three months. The drug content of the formulation was checked and found to be slightly decreasing. This decrease may be attributed to the harsh environment (40^{0}C) maintained during the studies.

Summary: The preformulation studies indicated that the absorption maximum of Bosentan monohydrate drug was 270 nm which corroborated with literature value. Calibration curve showed high degree of linearity indicated by regression value 0.999 which in turn represents the sensitivity and accuracy of developed UV analytical method. The developed analytical method is used for the drug estimation during *in vitro* drug release studies. Bosentan monohydrate gastroretentive tablets were formulated by wet granulation method. The powder blend exhibited uniform bulk density and tapped density in the range of 0.4-0.44gm/ml & 0.52-0.56gm/ml. This showed suitability of powder blend for tablet compression. The Bosentan monohydrate powder blend showed hausner's ratio, compressibility index and angle of repose in the range of 1.23-1.28, 18-22% and 27-32°c respectively. Preformulation

parameters study revealed that all results were within the ideal limits indicated the suitable flow properties ideal for tablet compression. Post compression parameters like weight uniformity 200mg, thickness 3.22-3.55mm, hardness 3.98-4.16kg/cm², friability <0.2% revealed all the developed formulations was uniform with respect to their post compression properties. All floating tablets exhibited floating lag time < 90 sec and duration of floating time 8-12 hrs respectively. Floating parameters indicated floating ability and prolonged floating duration for gastroretentive delivery of Bosentan monohydrate. Drug content studies revealed that all formulations showed uniform drug content in the range of 99-100%. *In vitro* release indicated that the drug release sustained for 8-12 hr which is suitable for prolonged action of the drug which guarantees better absorption and patient compliance.

CONCLUSION

From the current work it was evident that Bosentan monohydrate gastroretentive tablets were formulated and evaluated for their properties. The developed tablets exhibited characteristics which are in accordance with the official limits. All the formulations were found to be good indicating that the powder blend has good flow properties. Among all formulations the formulation S6 with HPMC K15M produced maximum drug release compared to others hence it was considered as the optimized formulation. The optimized formulation dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed zero order kinetics of drug release. Hence we conclude that Bosentan monohydrate gastroretentive tablets cold be formulated for regeoselective drug delivery from stomach for better absorption and improved drug action for prolonged time intervals.

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