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RESEARCH ARTICLE

Simultaneous Formulation Development, Evaluation and Estimation of Innovative Controlled Release Tablets of Bosentan Formulated with Varied Polymers

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ABSTRACT:
Bosentan is an endothelial receptor antagonist (ERA) indicated for the treatment of Pulmonary arterial hypertension (PAH). The aim of the present study involves the development of controlled release tablets of bosentan[1]. The tablets were prepared to release the drug for a prolong period of time within the GIT, to enhance the bioavailability, to minimize the dosing frequency, and to improve the patient compliance[2]. The tablets were formulated by using various polymers like hydroxyl propyl methyl cellulose, acacia and xanthum. The formulated tablets were evaluated[3]. The drug release from the optimized formulation (F7) was found to be the best after observing the results of dissolution rate and pre &post formulation studies[4].

KEYWORDS: Controlled release, Hydroxyl Propyl Methyl Cellulose (HPMC), bioavailability, Endothelial Receptor Antagonist (ERA), Pulmonary Arterial Hypertension (PAH), Gastro-intestinal tract (GIT).

1. INTRODUCTION:
The oral route of drug delivery is one of the most convenient means to administer drug to the human body to obtain the desired therapeutic effect[5]. Though it is a convenient route it provides several challenges to the formulator to design a medication such that it provides the drug in an optimum concentration needed to attain a plasma level of the drug which will fall within the therapeutic window to obtain the desired effect[6].

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Conventional therapy
Drug delivery classically has been via the oral route where the dosage forms release the drug as they dissolve in the gastrointestinal tract[7]. These delivery systems typically provide for rapid release of the active substance, which leads to a rapid increase in the concentration of the drug followed by the rapid decline in the drug content as the drug is metabolized and eliminated from the body[8]. However such behavior has the following problems:

1) At the maximal concentrations many drugs are highly toxic.
2) The therapeutically effective dose is maintained only for a very short period of time and hence multiple doses of the drug are required
3) Since release of the drug substance cannot be controlled, it may not be effectively delivered to the site of action in the body[27-43].

Conventional dosage forms are unable to control either the rate of delivery or obtain desired site of delivery[9]. As a result, there is a large redistribution of the drug to the non target tissues which exceeds the amount needed for the therapeutic activity which often leads to serious adverse events in the treatment[10].

Conventional dosage forms are rapidly absorbed with "peak" and "valley" or "saw tooth" kinetic plasma concentration profiles. Controlled delivery systems have been introduced to overcome all these above stated disadvantages of the conventional release systems[11].

Modified release drug delivery systems

The United States Pharmacopoeia definition of a Modified Release system is that:

"The drug release characteristics of time, course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms" [27-43].

These may be divided conveniently in to four categories

1. Delayed release
2. Controlled release
   a) Sustained release
   b) Extended release
3. Site specific targeting
4. Receptor targeting[12]

Table 1: Classification of oral controlled release systems:

TYPE OF SYSTEM	RATE CONTROLLING MECHANISM
Diffusion Controlled	
• Reservoir system	Diffusion through a membrane
• Monolithic system	
Water permeation controlled	
• Osmotic systems	Osmotic transport of water through a semi permeable membrane
• Swelling systems	Water penetration into a glassy polymer
Chemically Controlled	
• Monolithic system	Either pure polymer erosion (surface erosion) or a combination of erosion and diffusion(bulk erosion)
• Pendent systems	Combination of hydrolysis of the pendent group and diffusion from the bulk polymer
• Ion exchange resins	Exchange of acidic or basic drugs with ions present on resins
Regulated systems	
• Magnetic, Ultrasound	External application of magnetic field or ultrasound device
• Chemical	Use of competitive desorption or enzyme substrate reactions. Rate control is built into the device.

Drugs Suitable for CR Formulations

There are certain properties of the drug, which must be considered for the design of CR peroral dosage forms. The aqueous solubility and intestinal permeability of drug compounds are of paramount importance. A drug that is highly soluble at intestinal pH and absorbed by passive diffusion has an ideal characteristic for fabrication of CR dosage forms. A drug with no site-specific absorption characteristic is preferred. A drug with low aqueous solubility (<1 mg ml $^{-1}$) may already possess inherent sustained release (SR) potential[13].

2. MATERIALS AND METHODS

Table 2: The Materials used in the preparation of tablets

S NO	Materials	Name of the supplier
1	Bosentan	Chandra labs, HYD
2	HPMC	MYL CHEM Mumbai
3	Xanthan gum	MYL CHEM Mumbai
4	Acacia	MYL CHEM Mumbai
5	Ethyl cellulose	MYL CHEM Mumbai
6	MCC	MYL CHEM Mumbai
7	Magnesium Stearate	MYL CHEM Mumbai
8	Talc	S.D Fine chem. LTD Mumbai

Table 3: The Equipments used in the present work

S.No	Instruments	Source
1	Electronic balance	Shimadzu
2	UV/Visible Spectrophotometer	Corporation-BL-220H
3	FTIR spectrophotometer	Corporation Japan
4	Magnetic stirrer	Remi Motor Equipments
5	Dissolution apparatus	Shimadzu
6	Oven	Biotech India.
7	pH meter	Shital Scientific Industries
8	Compression machine	Cadmach Machinery

METHODOLOGY

PREFORMULATON STUDIES

Construction of Standard Graph of Bosentan in 0.1N HCl

Preparation of 0.1N HCl

Take 8.5ml of Hcl in distilled water and make up to 1000ml with distilled Water to get 0.1N HCl

Preparation of Standard solution in 0.1 N HCl:

Weigh accurately 100 mg of Bosentan was dissolved in 100 ml of volumetric flask using dissolution medium (0.1 N HCl) which gives concentration of 1000 µg/ml. Then 1ml of stock solution was taken and diluted to 100

ml which gives a concentration of 10 µg/ml. (Stock solution)

From this stock solution subsequent dilutions were made in 0.1 N HCl in order to get 2µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml, 10 µg/ml, Absorbance of these solutions were measured at λ max 204nm using UV-Visible spectrophotometer and standard curve was plotted.. The linearity plot was obtained for the aliquot concentration of 2, 4, 6, 8; 10µg/ml with the absorbance was seen at 204nm[14-16].

Preparation of Standard solution in Phosphate buffer pH 6.8:

Weigh accurately 100 mg of Bosentan was dissolved in 100 ml of volumetric flask using dissolution medium (phosphate buffer) which gives concentration of 1000 µg/ml. Then 1ml of stock solution was taken and diluted to 100 ml which gives a concentration of 10 µg/ml[27-43]. (Stock solution)

From this stock solution subsequent dilutions were made in phosphate buffer ph 6.8 in order to get 2µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml, 10 µg/ml, Absorbance of these solutions were measured at λ max 204nm using UV-Visible spectrophotometer and standard curve was plotted.. The linearity plot was obtained for the aliquot concentration of 2, 4, 6, 8; 10µg/ml with the absorbance was seen at 204nm[17].

Drug-excipient compatibility studies:

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. The IR spectrum of the physical mixture was compared with that of the pure drug to check any possible drug-excipient interaction[18].

Formulation of tablet:

Tablets prepared by direct compression method.

Manufacturing Procedure:

1) Micro crystalline cellulose, HPMC, Xanthan gum, Ethyl cellulose, Acacia were weighed according to the given table 4 and sifted through 40 mesh.
2) To the above blend Bosentan was added and sifted through 18 mesh.
3) The sifted materials were mixed for 10min.
4) Magnesium Stearate was weighed and sifted through 40 mesh.
5) To the powdered blend, lubricated blend was added and mixed properly[19].

The lubricated blend was compressed using 9mm round punches

Table 4: Formulation table

Ingredients (%)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Bosentan**(mg)**	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5
HPMC	10%	20%	30%	10%	20%	30%	10%	20%	30%
Xanthan gum	10%	20%	30%	--	--	--	-	-	--
Acacia	--	--	--	10%	20%	30%	--	-	--
Ethyl cellulose	--	--	--	--	--	--	10%	20%	30%
MCC	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Magnesium Stearate	2%	2%	2%	2%	2%	2%	2%	2%	2%
Talc	2%	2%	2%	2%	2%	2%	2%	2%	2%
Total wt	200	200	200	200	200	200	200	200	200

Coating with semi-permeable polymer:

Core tablets were coated by using a coating machine with a perforated pan. A solution of cellulose acetate in acetone at a concentration of (4%w/v), containing TEC at concentration of 10% of w/w of cellulose acetate, level of plasticizer (TEC) was used as the coating solution[20]. To the acetone, slowly cellulose acetate added with proper mixing. In between, plasticizer was added drop wise and through mixing was done to dissolve the cellulose acetate[21]. Addition of plasticizer in the coating solution improves film properties like film flexibility. The final coating solution was filtered through # 80 sieve. The composition solution used is mentioned in table 5 below:

Table 5: Coating solution composition

INGREDIENTS	Weight	CONCENTRATION (%)
Cellulose acetate	40gms	4%
Triethyl citrate	4 gms	0.4
Acetone	1000ml	Quantity sufficient

Core tablets of Bosentan were placed in coating pan and tablets were coated using the following parameters:

Pan rpm : 10-11
Coating solution spray rate : 4-5ml/min
In let temperature : 38°C
Outlet temperature : 28°C
Atomizer pressure : 1.0 kg/cm^2
Fan pressure : 1-0.75 kg/cm^2
Inlet air blower : 900 cpm
Outlet air blower : 1600 cpm

The coating solution was sprayed over the tablet bed by a spray gun till a desired weight gain was obtained on the active core tablets .Later the osmotic pump tablets were dried at 50°C for 1 Hr to remove the residual organic solvent[22].

Pre-compression parameters

a) Angle of repose.
b) Bulk density and Tapped density.
c) Hausner ratio.
d) Compressibility index (%)

Micromeritic properties:

a) Angle of repose (Θ):

The angle of repose of powdered blend was determined by the funnel method. The accurately weight 15gm powdered blend was taken in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the blend. The powdered blend was allowed to flow through the funnel freely on to the surface[27-43]. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$\tan \theta = h/r$

Where, h –height of the powder cone
r - radius of the powder cone

Different ranges of flow ability in terms of angle of repose are given below.

Table 6: Relationship between angle of repose (Θ) and flow properties.

Angle of repose value	Flow property
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

b) Bulk density and tapped density:

Both loose bulk density (LBD) and Tapped bulk density (TBD) were determined. A quantity of 15gm of granules from each formula, previously shaken to break any agglomerates formed, was introduced in to 50ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at sec intervals. Tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following equations.

LBD = Weight of the powdered blend /bulk volume
TBD = Weight of the powdered blend /true volume

c) Hausner's factor

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula

Hausner's factor = Tapped density/Bulk density

d) Carr's compressibility index:

The compressibility index of the granules was determined by Carr's compressibility index. (%) Carr's Index can be calculated by using the following formula

Compressibility % = [(TD - BD)/ TD] ×100

Table 7: Compressibility index

Compressibility index	Flow property
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to passable
23 – 35	Poor
33 – 38	Very poor
>40	Very very poor

Evaluation of osmotic tablet

Hardness

This is the force required to break a tablet in diametric compression. Hardness of the tablets is determined by Monsanto hardness tester which consists of a barrel with a compressible spring. The pointer moving along the gauge in the barrel at which the tablet fractures.

Weight variation

Ten tablets were selected at random and average weight was determined. Then individual tablets were weighted and the individual weight was compared with an average weight. Not more than two of the individual weights deviate from the official standard (limit ± 5%).

Tablet size and Thickness

The size and thickness of the tablets were measured by using Vernier Calipers scale.

Drug content analysis

Five tablets weighted and crushed in a mortar then weighed powder contained equivalent to 200 mg of drug transferred in 100ml of phosphate buffer to give a concentration of 100µg/ml. Take 15ml of this solution and diluted it up to 100ml with phosphate buffer to give a concentration of 15µg/ml. Absorbance measured at 204nm using UV- visible spectrophotometer.

***In vitro* dissolution studies**

Dissolution rate of osmotic tablets from all formulations were performed using LAB INDIA dissolution apparatus (USP II) with paddle. The dissolution fluid was 900 ml 0.1N HCL for first 2hrs then replaced with phosphate buffer pH 6.8 at a speed of 50 rpm and a temperature of 37º C were used in each test[24]. The dissolution

experiments were conducted in triplicate. For all tests 5ml samples of the test medium were collected at set intervals (1, 2, 4, 6, 8, 10, 12hrs) and were replaced with equal volume of phosphate buffer pH 6.8. The samples were analyzed at 204nm using a UV spectrophotometer[23].

***In vitro* drug release studies**

Apparatus used **:** USP II dissolution test apparatus
Dissolution medium volume : 900 ml
Volume temperature : $37^o \pm 0.5^o$ C
Speed of basket paddle : 50 rpm
Sampling intervals : (1, 2, 3, 4, 6, 8, 10 and 12 hrs)
Sample withdrawn : 5 ml
Absorbance measured : 204nM

Kinetic Analysis of Dissolution Data

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration[25]. The first order Eq. (2) describes the release from system where release rate is concentration dependent, Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets (Hixson and Crowell, 1931).

$$C = K_0 t \qquad (1)$$

Where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$LogC = LogC_0 - K_1 t / 2.303 \qquad (2)$$

Where, C_0 is the initial concentration of drug and K_1 is first order constant.

$$Q = K_H t^{1/2} \qquad (3)$$

Where, K_H is the constant reflecting the design variables of the system.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} t \qquad (4)$$

Where, Q_t is the amount of drug remained in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson-Crowell rate equation.

The following plots were made using the in-vitro drug release data

Cumulative % drug release vs. time (Zero order kinetic model);
Log cumulative of % drug remaining vs. time (First order kinetic model);
Cumulative % drug release vs. square root of time (Higuchi model);

And cube root of initial concentration minus the cube root of percentage of drug remaining in the matrix vs. time (Hixson-Crowell cube root law).

Mechanism of drug release

Korsmeyer *et al* (1983) derived a simple relationship which described drug release from a polymeric system Eq. (5). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model.

$$M_t / M_\infty = Kt^n \qquad (5)$$

Where $M_t / M\infty$ is fraction of drug released at time t, K is the release rate constant incorporating structural and geometric characteristics of the tablet, and n is the release exponent. The n value is used to characterize different release mechanisms[27].

A plot of log cumulative % drug release vs. log time was made. Slope of the line was n. The n value is used to characterize different release mechanisms as given in table 8, for the cylindrical shaped matrices. Case-II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release[26].

Table 8: Diffusion Exponent and Solute Release Mechanism for Cylindrical Shape

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

3. RESULTS AND DISCUSSIONS

Preformulation studies

Description

These tests were performed and the results were illustrated in the following table 9:

Table 9: Table showing the description of Bosentan (API)

Test	Description
Colour	White to off white powder
Odour	Free of odour

Result

The results were found as per specifications**.**

Solubility

These tests were performed and the results are illustrated in the table 10

Table 10: Solubility of Bosentan (API) in various solvents.

Solvents	Solubility
Water	soluble
pH6.8 Phosphate buffer	Soluble
Methanol	Soluble
Chloroform	Soluble

Melting Point

This test is performed and the result was illustrated in the following table 11.

Table 11: Melting point of API's

Material	Melting Point
Bosentan	138^0c

Result: The Result was found to be within limit.

Preparation of Standard curve

Table 12: Calibration curve data of Bosentan in 0.1N HCl

CONCENTRATION (µg /ml)	ABSORBANCE
0	0
2	0.102
4	0.214
6	0.363
8	0.475
10	0.555

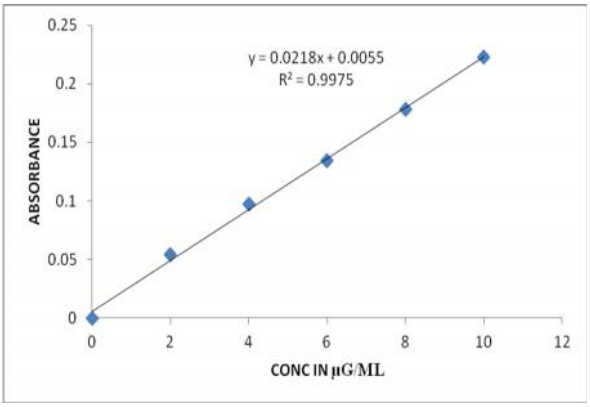

Figure 1 : Calibration cuve plot of Bosentan in 0.1N HCL

Table 13: Calibration curve data of Bosentan in phosphate buffer pH6.8

CONCENTRATION (µg /ml)	ABSORBANCE
0	0
2	0.054
4	0.097
6	0.134
8	0.178
10	0.223

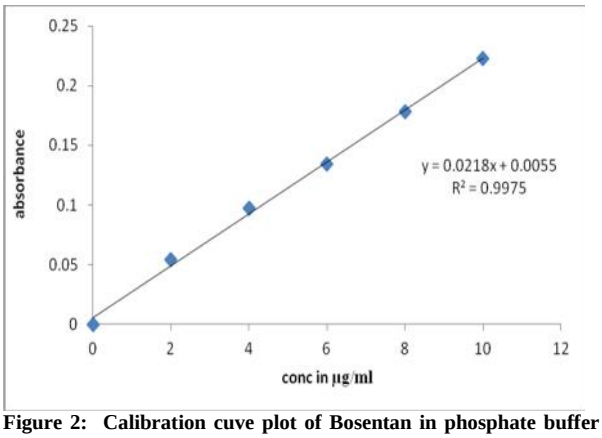

Figure 2: Calibration cuve plot of Bosentan in phosphate buffer pH6.8

Drug-Excipient Compatibility study by FTIR:

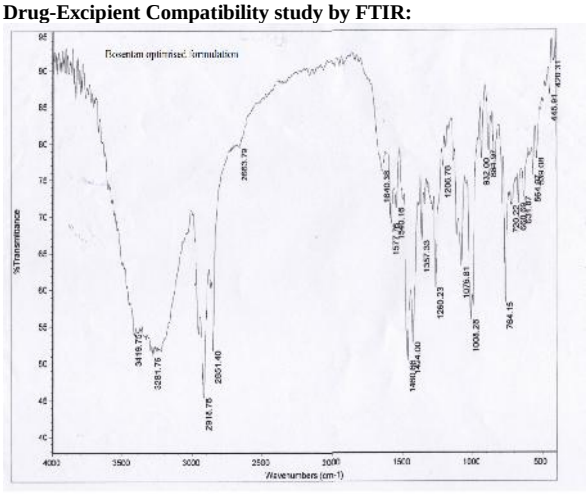

Figure 3: FTIR of Bosentan pure drug

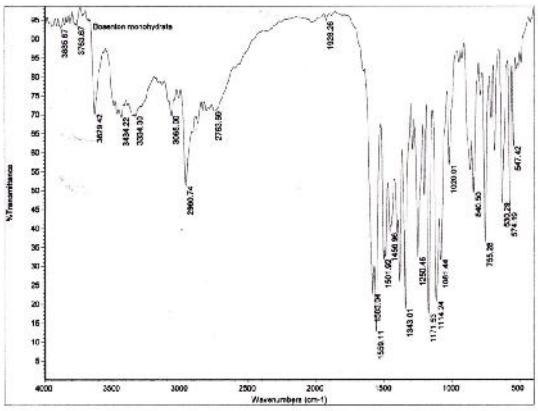

Figure 4: FTIR of Bosentan optimized formulation

PRE-COMPRESSION PARAMETERS:

Table 14: Preformulation parameters of Bosentan tablets prepared by direct compression method.

S.no	Formulations	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Compressibility index (%)	Angle of repose 0	Haunser ratio
1	F1	0.44	0.52	15.38	25.10	1.18
2	F2	0.42	0.49	14.29	26.79	1.17
3	F3	0.43	0.51	15.69	24.54	1.19
4	F4	0.41	0.48	14.58	27.56	1.17
5	F5	0.44	0.52	15.38	25.38	1.18
6	F6	0.43	0.50	14.00	28.10	1.16
7	F7	0.48	0.56	14.29	25.49	1.17
9	F8	0.47	0.54	12.96	24.57	1.15
10	F9	0.45	0.53	15.09	26.45	1.18

a. Bulk density and tapped density

Bulk density and tapped density of powder blend was evaluated. The results were shown in the table 14.

b. Angle of Repose

The angle of repose for the entire formulations blend was evaluated. The results were shown in the table 14 range from 25.10-28.58.

c. Compressibility Index

Compressibility index for the entire formulations blend was evaluated. The results were shown in the table 14 range from.12.96-15.69

d. Hausner`s Ratio

The Hausner`s ratio for the entire formulations blend was evaluated. The results were shown in the table 14 range from 1.15-1.19. All these are within the limit.

Table 15: Post formulation parameters of tablets

Formula code	Hardness (Kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)
F1	5.2	200	0.26	99.6
F2	5.4	199	0.35	99.0
F3	5.0	200	0.28	99.4
F4	5.9	202	0.33	99.3
F5	5.8	198	0.28	99.2
F6	5.0	200	0.5	99.5
F7	5.2	201	0.45	99.8
F8	5.1	199	0.35	99.1
F9	5.0	199	0.35	99.4

EVALUATION OF TABLETS

HARDNESS

The prepared tablets in all the formulations possessed good mechanical strength with sufficient hardness in the range of 6.8 to 7.4 kg/sq cm. (as shown in table no.15)

FRIABILITY

Friability values below 1% were an indication of good mechanical resistance of the tablets.

WEIGHT VARIATION

All the tablets from each formulation passed weight variation test, as the % weight variation was within the pharmacopoeial limits of ±5% of the weight. The weight variation in all the nine formulations was found to be 198 to 202 mg, which was in pharmacopoeial limits of ±5% of the average weight. (as shown in table no 15)

DRUG CONTENT

The percentage drug content of all the tablets was found to be around 99 % which was within the acceptable limits. (as shown in table no 15)

DISSOLUTION STUDIES FOR TABLETS

Table 16: Rate of Dissolution of various formulations

Time in hrs	F1	F2	F3	F4	F5	F6	F7	F8	F9
30min	10.1	10.9	7.1	29.4	28.5	4.9	5.1	6.1	6.8
1	38.9	20.27	16.9	59.1	69.8	10.1	11.5	15.2	16.4
2	70.1	29.16	28.7	100.1	100.3	21.4	20.1	25.9	28.6
4	100.1	39.41	50.1	--	--	29.6	30.3	40.1	49.3
6	--	56.71	73.2	--	--	49.8	48.2	60.1	72.8
8	--	64.76	99.2	--	--	64.1	61.5	89.1	99.10
10	--	73.18	--	--	--	85.9	88.1	99.4	--
12	--	86.12	--	--	--	90.3	100.1	--	--

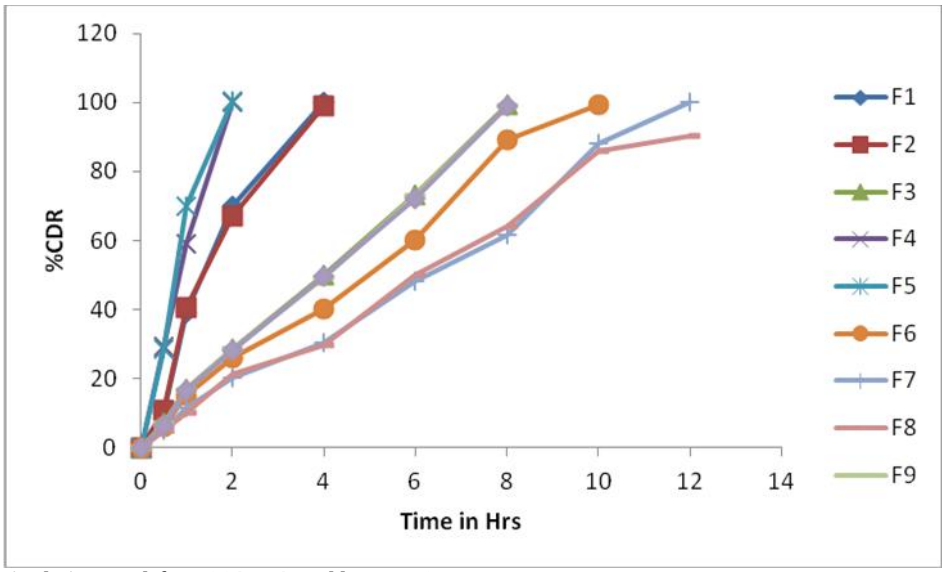

Figure 5: Dissolution graph for BOSANTAN tablets F1- F9

It is evident that after coating with semipermeable membrane of Cellulose acetate, the increase in concentration of osmogen KCl leads to increase in drug release from the tablet. Among all formulations F7 was optimized based on maximum drug release

KINETIC STUDIES FOR OPTIMIZED FORMULATION (F7)

Table 17: Release kinetics for the optimized formulation F7

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	8.19388201	-0.137180696	33.70717007	1.323782148
Intercept	1.05826657	2.251585847	-26.1231688	0.636149264
Correlation	0.99532751	-0.871328514	0.972807289	0.881205332
R 2	0.990676853	0.759213379	0.946354021	0.776522837

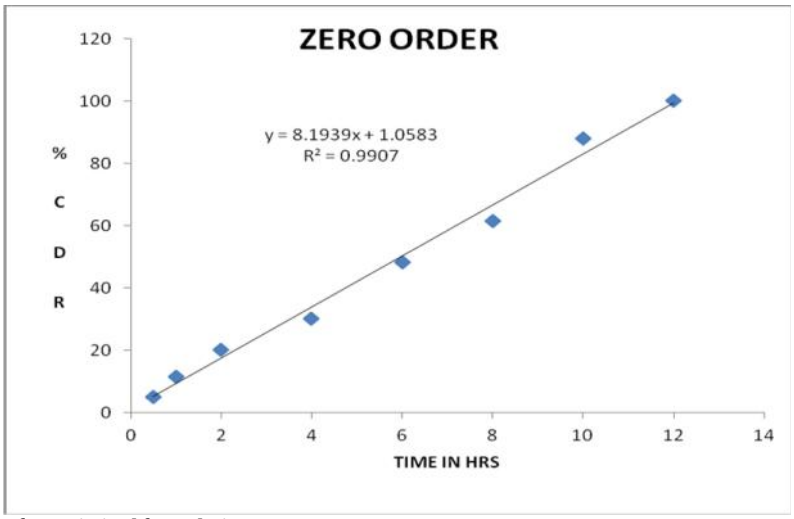

Figure 6: Zero order plot for optimized formulation

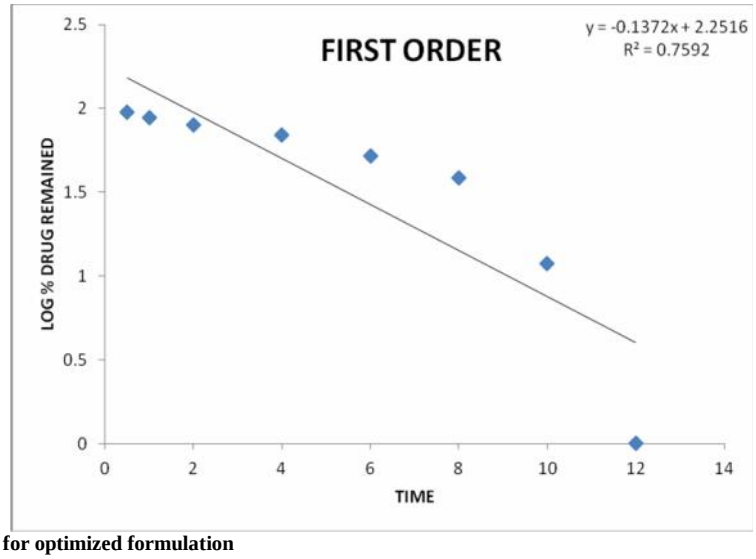

Figure 7: First order plot for optimized formulation

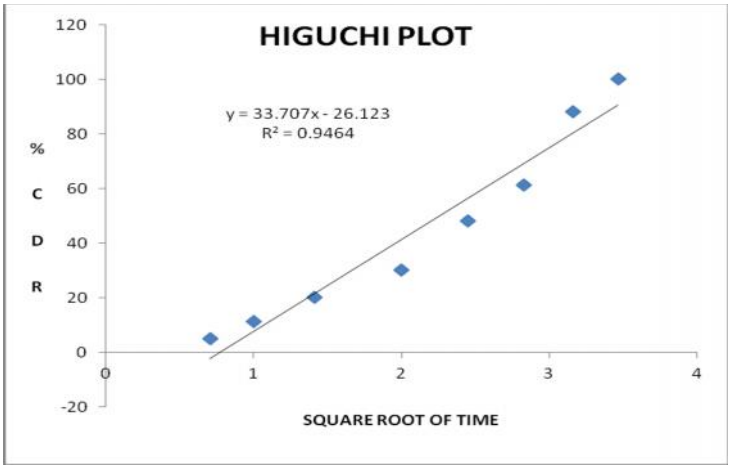

Figure 8: Higuchi plot for optimized formulation

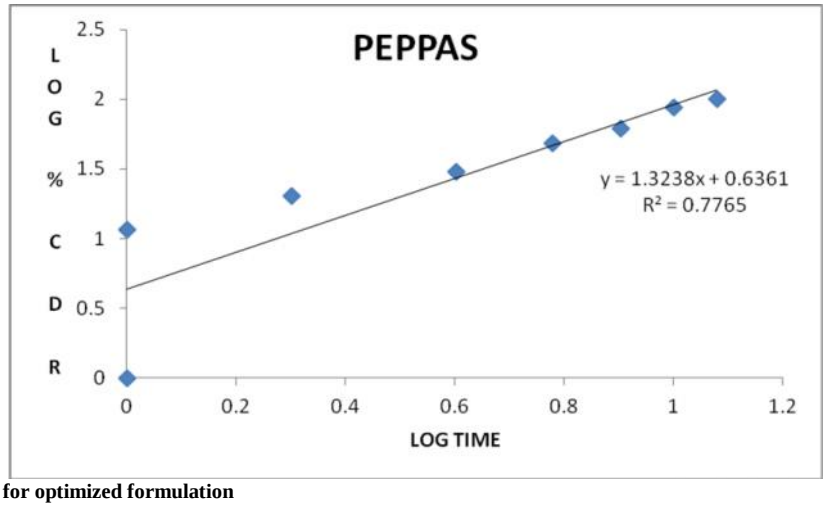

Figure 9: Peppas plot for optimized formulation

4. SUMMARY AND CONCULSION:

In the present work, an industrially important project entitled "Formulation and Evaluation of Bosentan Controlled Release Tablets" was undertaken. The study was undertaken with an aim to formulate Bosentan as Controlled release tablets. During this phase of investigation various factors that likely to affect the performance of the controlled release was studied. The release kinetics, dissolution rate, process variables such as hardness, weight variation during granulation are the factors found critical during the development based on the experimental finding. Preformulation studies were done initially and results directed the further course of formulation. With the data literature review, preformulation and prototype formulation trails were started. Direct compression, Wet granulation method was formulated. Granules were evaluated for tests such as bulk density, Tapped density, Compressibility Index and Hausner ratio before being punched as tablets. Tablets were tested for weight variation, thickness and friability, *in-vitro* dissolution tests were performed and percentage drug release was calculated. Dissolution tests were performed and percentage drug release was calculated. Dissolution profile of Formulation – F7 was optimized based on evaluation parameters. In the dissolution modeling all the developed formulations followed Korsemeyer-peppas drug release. The optimized formulation F7 followed zero order drug release and Korsemeyer-peppas release kinetics model i.e super case II transport. The developed formulation was tested for its stability for three months and found to be stable. In the present study, polymethacrylates were found to play a great role in controlling release of drug Bosentan from the osmotic system. Accordingly, it can be concluded that the formulation is robust in the performance is less likely to be affected by the various factors studied.

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