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Formulation and *In-vitro* Evaluation of Bosentan Sustained Release Tablets

Ruqsar Unnisa*
Dr. Sridhar Babu R
Syed Rahmath Ali

Department of Pharmacy, Shadan College of Pharmacy, Hyderabad, India

Abstract

Model drug used in present investigation has relatively short plasma half-life and low bioavailability (~50%). Two to three times administration was required for larger doses, this can decrease the patient compliance. Sustained release formulation maintains plasma level for 10-12hrs and it might be sufficient for daily dosing of bosentan. Main objective of the present investigation was to develop an oral sustained release bosentan formulation by using different polymers in combination with Hydroxy propyl methyl cellulose (HPMC). Tablets were prepared by direct compression method. In vitro dissolution studies were carried out for all nine formulations in simulated gastric fluid using USP type II dissolution apparatus for 10-12hrs. Dissolution data was analyzed using different kinetic models. B7 formulation with combination of polymers HPMC and ethyl cellulose (EC) shows sustained drug release upto 12hrs. Kinetic modeling of In-vitro drug release study of optimized formulation indicates dissolution follows zero order, fitting dissolution data to higuchi model revealed super case II transport.

Keywords: Hydroxy propyl methyl cellulose, Sustained release, Simulated gastric fluid, Kinetic models, Ethyl cellulose.

Introduction

Most conventional oral drug products, such as tablets and capsules, are formulated to release and complete systemic drug absorption immediately after oral administration of prodrug. Such immediate release tablets result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. In recent years, various modified-release drug products have been developed to control the release rate of the drug and/or the time for drug release [1].

The term modified-release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined "as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions or promptly dissolving dosage forms as presently recognized" [2-5].

Several types of modified-release drug products are recognized

Extended-release drug products: A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of prolonged-release dosage forms include controlled-release, sustained-release, and long-acting drug products [6].

The term controlled-release drug product was previously used to describe various types of oral extended-release-rate dosage forms,

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***Corresponding author:** Ruqsar Unnisa, Department of Pharmacy, Shadan College of Pharmacy, Peerancheru, Himayat Sagar Road, Hyderabad, India. Tel: +8688375127; Email: ruksarunnisa087(at)gmail.com

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including sustained-release, sustained-action, prolonged-action, long-action, slow-release, and programmed drug delivery [7].

Sustained drug release (SR): The goal of sustained –release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period. Commonly, the release rate of drug is not altered and does not result in sustained delivery once drug release has begun [8-10].

Classification of oral sustained release systems

A. Diffusion Sustained Systems: Reservoir devices and Matrix devices

B. Dissolution controlled systems: Matrix systems and Encapsulation systems

C. Diffusion and Dissolution Controlled System: In a bio-erodible matrix, the drug is homogenously dispersed in a matrix and it is released either by swelling controlled mechanism or by hydrolysis or by enzymatic attack [11-14].

Materials and Methods

Materials

Bosentan drug was gifted sample from Chandra labs, Hyderabad. Polymers Hydroxy propyl methyl cellulose (HPMC), Ethyl cellulose (EC), Xanthan gum, Acacia were purchased from MYL chemicals, Mumbai. Micro crystalline cellulose (MCC), Magnesium stearate and Talc were laboratory standards.

Methodology

Pre-formulation studies: ***4.2.1.1 Analytical study:*** *Drug description, solubility studies in different solvents, determination of melting point and scanning of drug using UV Visible spectrophotometer.*

Construction of standard graph of Bosentan in 0.1N HCL: *Bosentan drug dissolved in 0.1N HCL and preparae concentrations from 2-10 µg/ml and absorbance were noted at 204nm using UV Visible spectrophotometer. Linearity graph was plotted with these observations against concentrations.*

Construction of linearity curve of Bosentan in pH 6.8 Phosphate buffer: *2-10 µg/ml concentrations of drug solutions were prepared using pH 6.8 Phosphate buffer as solvent and note the absorbance for the same concentrations using UV Visible spectrophotometer at lamda max 204nm. Concentrations were plotted on X-axis and noted absorbance for respective concentrations were plotted on Y-axis to achieve calibration curve.*

Drug – excipient compatibility study: The IR spectrum of the physical mixture was compared with that of the pure drug to check any possible drug-excipient interaction.

Formulation of sustained release tablets: ***4.2.3.1 Pre-compression parameters:*** *Mixed blend was evaluated for flow properties like Bulk density, Tapped density, Angle of repose, Hausner ratio and compressibility index.*

Preparation of Bosentan SR tablets: *Bosentan SR tablets were prepared using direct compression method shown in* ***table 1****.*

Evaluation of SR tablets: Prepared tablets were evaluated for Physical appearance, Size & shape, weight variation test, Friability, Hardness, Drug content and In-vitro dissolution studies.

In-vitro drug release studies: *Bosentan SR tablets dissolution studies were conducted in USP type II dissolution apparatus, first two hours in 0.1N HCL and remaining time for 6.8pH phosphate buffer to simulate in vivo gastric conditions.*

Kinetic analysis of dissolution data: To analyze the in vitro release data various kinetic models were used to describe the release kinetics: Zero order kinetics, First order kinetics, Higuchi plot and Kosmeyar Peppas model explained in table 2.

Results and Discussion

Pre-formulation studies

Drug description: Observations were found as per specifications only showed in table 3.

Solubility: Bosentan drug solubility increases with increasing the pH of the solvent and poorly soluble in water discussed in table 4.

Melting point: Bosentan (API) melting point was observed at 138^0c and within the limits only.

Scanning of API: Figure 1

Standard calibration curve of Bosentan

Figure 2 and Figure 3

Drug-excipient compatibility study (FTIR)

Figure 4 and Figure 5

Pre compression parameters of formulations

Table 5

Post compression parameters for formulations

Table 6

Table 1: Formulation table for Bosentan SR tablets.

Ingredients (%)	B1	B2	B3	B4	B5	B6	B7	B8	B9
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 (mg)	200	200	200	200	200	200	200	200	200

Table 2: 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

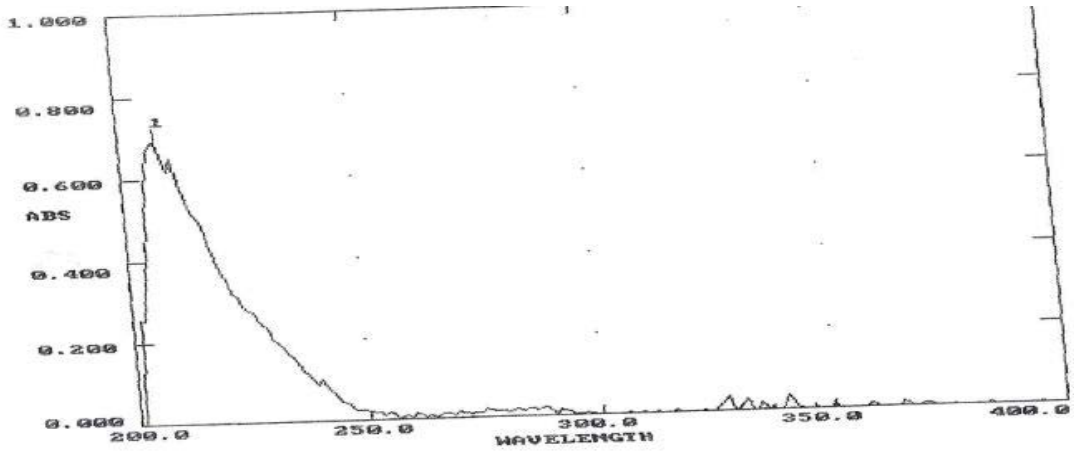

Figure 1: UV Spectrum for Bosentan observed at 204nm.

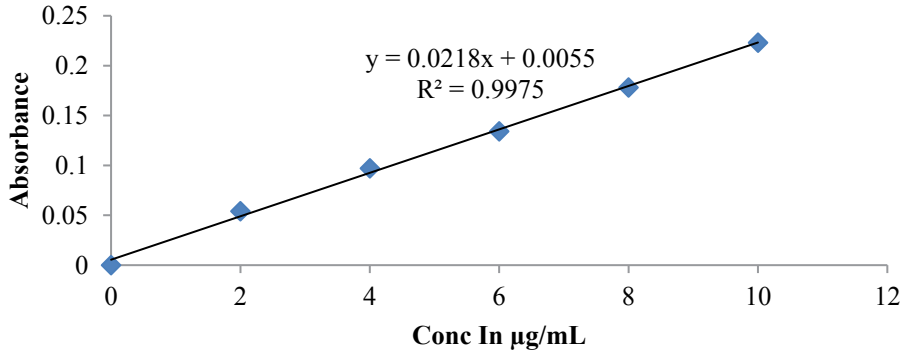

Figure 2: Calibration curve of Bosentan in 0.1N HCL.

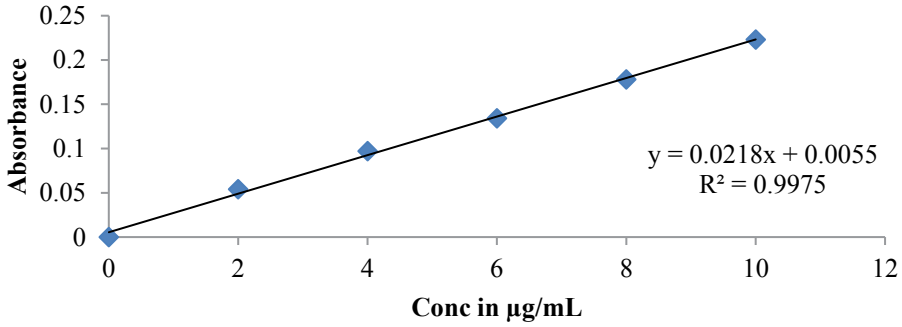

Figure 3: Calibration curve of Bosentan in pH 6.8 Phosphate buffer.

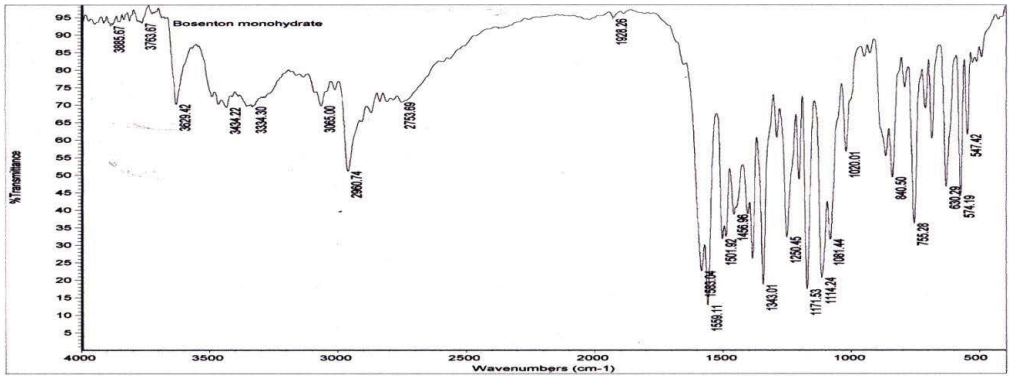

Figure 4: FTIR of Bosentan pure drug.

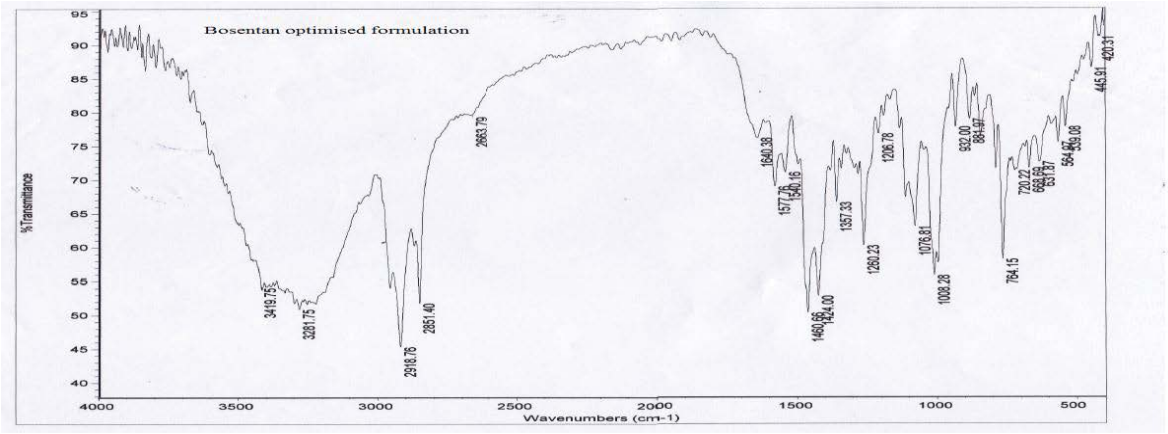

Figure 5: FTIR of Bosentan optimized formulation.

Table 3: Table showing the description of Bosentan (API).

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

Table 4: Table showing the Solubility of Bosentan (API) in various solvents.

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

Table 5: Precompression parameters of formulation blend.

S.no	Formulations	Bulk Density	Tapped Density	Compressibility	Angle of repose	Haunser ratio
		(gm/ml)	(gm/ml)	index (%)	(°)	
1	B1	0.44	0.52	15.38	25.10	1.18
2	B2	0.42	0.49	14.29	26.79	1.17
3	B3	0.43	0.51	15.69	24.54	1.19
4	B4	0.41	0.48	14.58	27.56	1.17
5	B5	0.44	0.52	15.38	25.38	1.18
6	B6	0.43	0.50	14.00	28.10	1.16
7	B7	0.48	0.56	14.29	25.49	1.17
8	B8	0.47	0.54	12.96	24.57	1.15
9	B9	0.45	0.53	15.09	26.45	1.18

Table 6: Post formulation parameters of tablets.

Formula code	Hardness (Kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)
B1	5.2	200	0.26	99.6
B2	5.4	199	0.35	99.0
B3	5.0	200	0.28	99.4
B4	5.9	202	0.33	99.3
B5	5.8	198	0.28	99.2
B6	5.0	200	0.5	99.5
B7	5.2	201	0.45	99.8
B8	5.1	199	0.35	99.1
B9	5.0	199	0.35	99.4

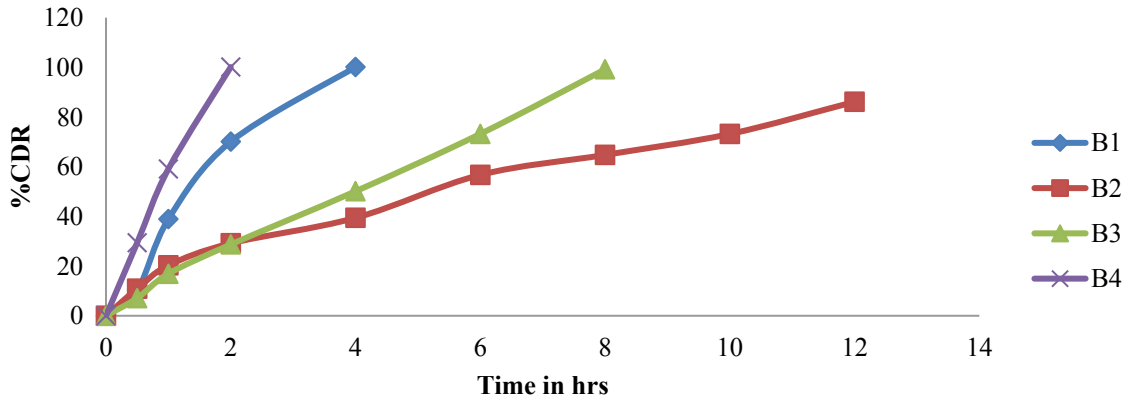

Figure 6: Dissolution profile of Bosentan formulations B1-B4.

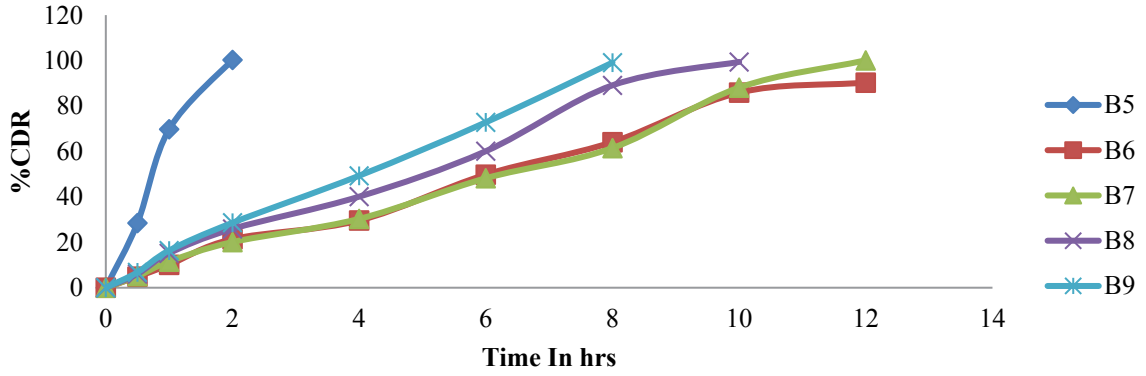

Figure 7: Dissolution profile of Bosentan SR formulations B5-B9.

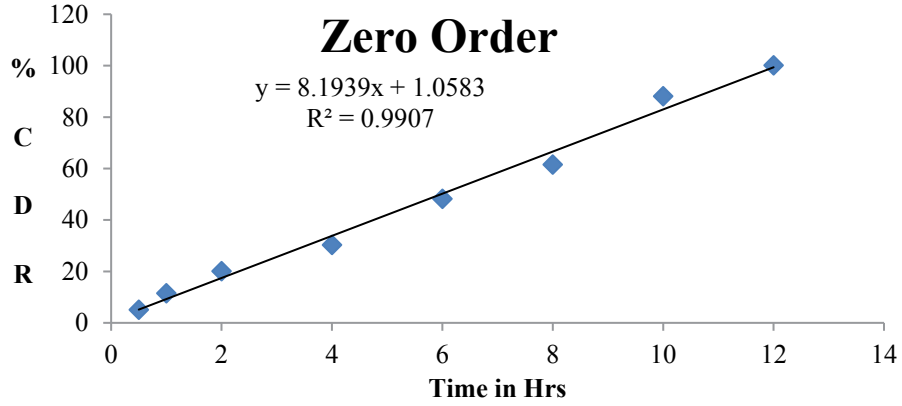

Figure 8: Zero order plot for B7 dissolution data.

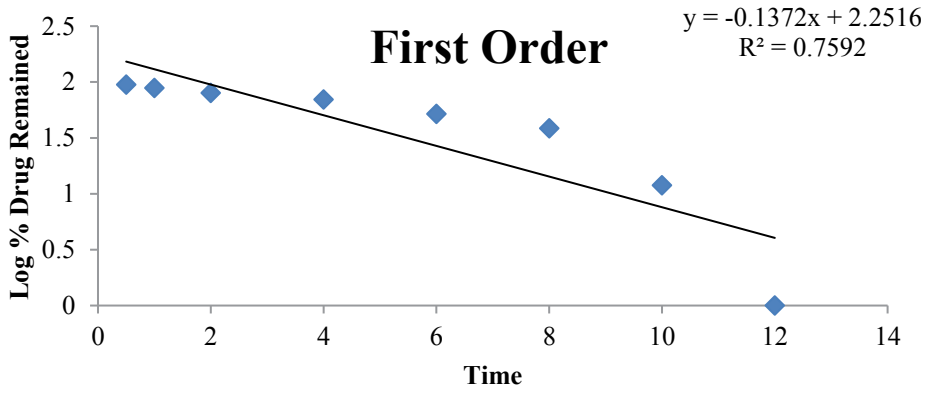

Figure 9: First order plot for B7 dissolution data.

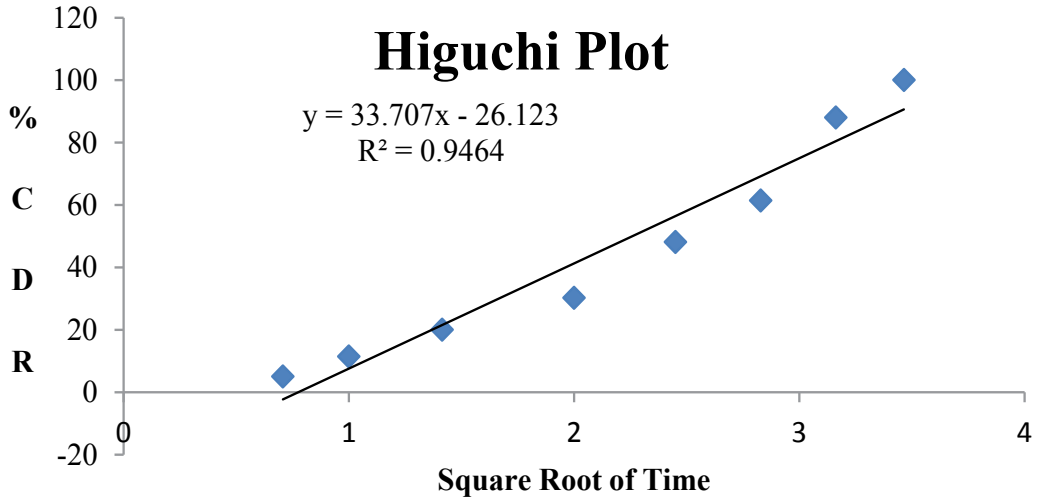

Figure 10: Higuchi modeling for B7 formulation data.

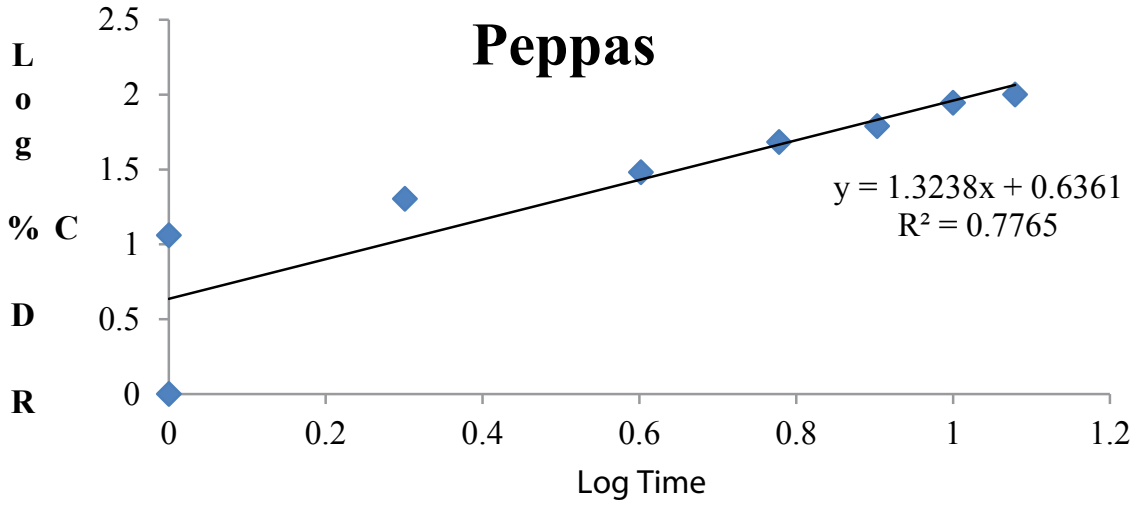

Figure 11: Peppas modeling for B7 formulation data.

In-vitro dissolution studies

Figure 6 and Figure 7

Kinetic studies for optimized formulation (B7)

Table 7 and Figures 8-11

Summary and Conclusion

Present study was undertaken with an aim to formulate Bosentan as Sustained release tablets. During this phase to investigate various factors those are affect the performance of the Sustained release was studied. Dissolution profile of Formulation – B7 was optimized based on evaluation parameters. The optimized formulation B7 followed zero order drug release and Higuchi release kinetics model i.e super case II transport. In the present study, polymers were found to play a great role in controlling release of drug Bosentan from the matrix 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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