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Formulation and *in vitro* evaluation of bosentan osmatic controlled release tablets

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ABSTRACT

In the present work, an industrially important project entitled "Formulation and *In vitro* Evaluation of Bosentan Osmotic Controlled Release Tablets" was undertaken. The study was undertaken with an aim to formulate Bosentan as osmotic controlled release tablets. During this phase of investigation various factors that likely to affect the performance of the osmotic controlled release was studied. The release kinetics, dissolution rate, process variables such as hardness, weight variation are some of the factors found critical during the development based on the experimental findings. Preformulation studies were done initially and results directed the further course of formulation. With the literature review data, Preformulation and prototype formulation trails were started. Direct compression method was used for formulation. 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 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 Korsemeyer-peppas drug release kinetics model i.e super case 2 transports and non-Fickian model. 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 and it is less likely to be affected by various factors studied.

INTRODUCTION

Modified release drug delivery systems

The *United States Pharmacopoeia* definition of an 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".

Delayed release systems

These systems are those repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release systems include repeat action tablets and capsules and enteric coated tablets where timed release is achieved by a barrier coating.

Controlled release systems

These systems also provide a slow release of drug over an extended period of time and also can provide some control, whether this be temporal or spatial nature, or both, of drug release in the body, or other words, the

system is successful at maintaining constant drug levels in the target tissue of cells.

Sustained release

These systems include any drug delivery system that achieves slow release of drug over an extended period of time.

Extended release

Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate & necessarily reduce the dosage frequency by two folds

Site specific targeting systems

These systems refer to targeting of drug directly to certain biological location in this case the target is adjacent to or in the diseased organ or tissue.

Receptor targeting systems

These systems refer to targeting of drug directly to certain biological location in this case the target is the particular receptor for a drug within an organ or tissue. Site specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be controlled drug delivery systems.

Potential Advantages of controlled drug therapy

All controlled release products share the common goal of improving drug therapy over that achieved with their non-controlled counter parts. This improvement in drug therapy is represented by several potential advantages of the controlled release systems are

Decreased local and systemic side effects

- Reduced gastrointestinal irritation.

Better drug utilization

- Reduction in the total amount of drug used.
- Minimum drug accumulation on chronic dosing/improved efficiency in treatment.
- Optimized therapy.
- More uniform blood concentration.
- Reduction in fluctuation in drug level and hence more uniform pharmacological response.
- Special effects e.g. sustained release aspirin provides sufficient drug so that on awakening the arthritic patient gets symptomatic relief cure or control of the condition more promptly. There is less reduction in the activity with chronic use.

Improved patient compliance

- Less frequent dosing.
- Reduced nighttime dosing.
- Reduced patient care time.
- Economy.

METHODOLOGY

PREFORMULATION 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

100 mg of bosentan was accurately weighed and transferred in a 100 ml volumetric flask. To this 100 ml of 0.1N HCl was added and shake well and to get a solution It concentration was 1000 µg/ml (stock solution 1).Then 1ml of stock solution was taken and diluted to 100 ml which gives a concentration of 10 µg/ml. (Stock solution 2) 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, 12 µg/ml ,14 µg/ml,16 µg/ml,18 µg/ml, Absorbance of these solutions were measured at λ max 269nm using UV-Visible spectrophotometer and standard curve was plotted . The linearity plot was obtained for the aliquot concentration of 2, 4, 6, 8, 10 12, 14, 16, 18µg/ml with the absorbance was seen at 269nm.

Preparation of Standard solution in Phosphate buffer pH 6.8

100 mg of bosentan was accurately weighed and transferred in a100 ml volumetric flask. To this 100ml of phosphate buffer pH 6.8 was added and shake well and to get a solution. It concentration was 1000 µg/ml(stock solution 1) . Then 1ml of stock solution was taken and diluted to 100 ml which gives a concentration of 10 µg/ml. (Stock solution 2) From this stock solution subsequent dilutions were made in phosphate buffer pH 6.8 in order to get 5µg/ml, 10 µg/ml, 15µg/ml, 20µg/ml, 25 µg/ml, 30 µg/ml, 35 µg/ml, 40 µg/ml, 45 µg/ml Absorbance of these solutions were measured at λ max 269nm using UV-Visible spectrophotometer and standard curve was plotted . The linearity plot was obtained for the aliquot concentration of 5 , 10 , 15 , 20 , 25 ,30 ,35 , 40 ,45 µg/ml with the absorbance was seen at 269nm.

MANUFATURING PROCEDURE

- Micro crystalline cellulose, osmotic agents, PVP K30 was weighed according to the given table no 1 and sifted through 40 mesh.
- To the above blend Bosentan was added and sifted through 18 mesh.
- The sifted materials were mixed for 10min.
- Magnesium Stearate was weighed and sifted through 40 mesh.
- To the powdered blend, lubricated blend was added and mixed properly.
- The lubricated blend was compressed using 9mm round punches

Table no 1: Various formulations of Osmatic controlled tablets were made as given table

Ingredients (%)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Bosentan **(mg)**	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5
Sodium chloride	0.5	-	-	-	-	-	-	-	-	-
Potassium chloride	-	0.5	-	-	-	0.75	1.0	1.25	-	-
Mannitol	-	-	0.5	-	-	-	-	-	0.75	1.0
Sucrose	-	-	-	0.5	-	-	-	-	-	-
Fructose	-	-	-	-	0.5	-	-	-	-	-
PVP K-30	5	5	5	5	5	5	5	5	5	5
MCC	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total wt	200	200	200	200	200	200	200	200	200	200

PRE-FORMULATION STUDIES

Description

These tests were performed and the results were illustrated in the following table no2

Table no 2: 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 following table no 3

Table no3: Table showing the 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 no 4.

Table no 4: Table showing the melting point of API's

Material	**Melting Point**
Bosentan	138°C

Result

The Result was found to be within limit.

PREPARATION OF STANDARD CURVE

Table no 5: calibration curve data of Bosentan in 0.1N HCl

CONCENTRATION (µg /ml)	ABSORBENCE
0	0
2	0.102
4	0.214
6	0.363
8	0.475
10	0.555
12	0.691
14	0.808
16	0.925
18	1.042

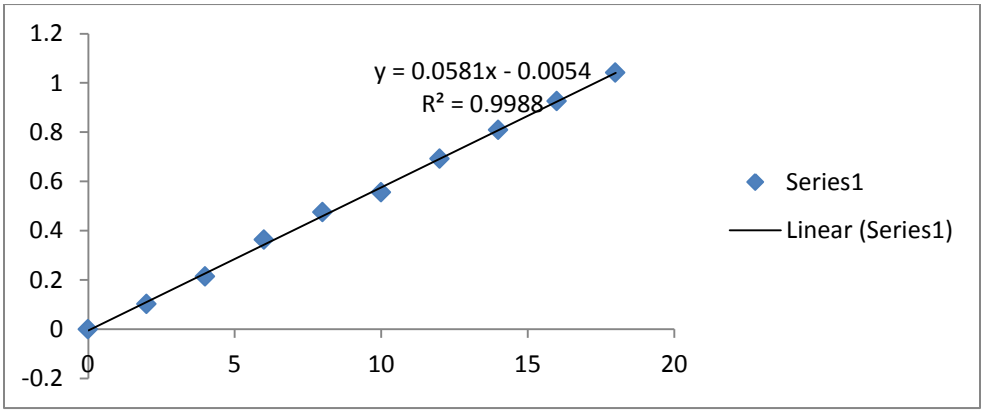

Fig no:1 caliberation curve plot of bosentan in 0.1N HCl

Table no :6 caliberation curve data of bosentan in phosphate buffer pH 6.8

CONCENTRATION (µg /ml)	**ABSORBENCE**
0	0
5	0.137
10	0.223
15	0.354
20	0.442
25	0.572
30	0.660
35	0.791
40	0.878
45	0.998

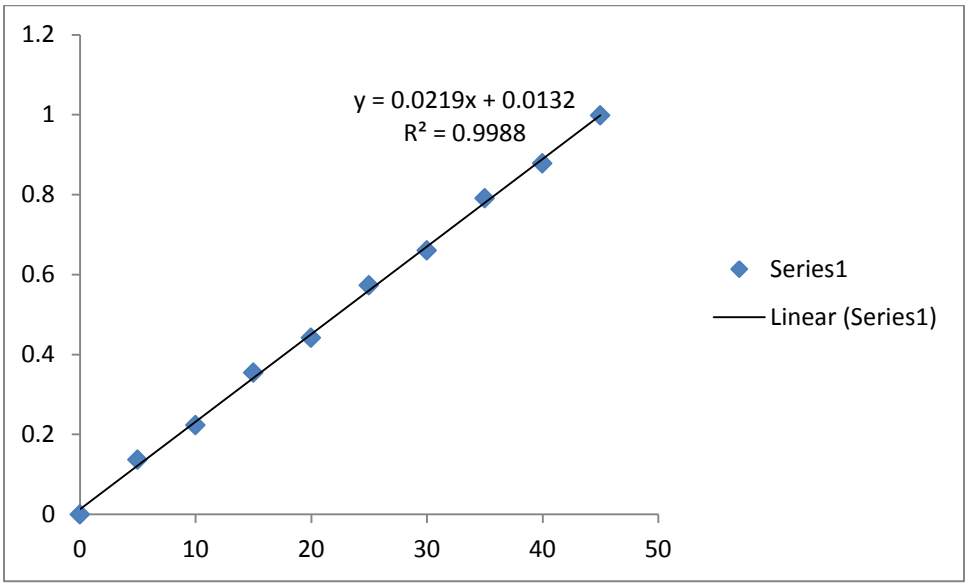

Fig no 2 Caliberation curve plot mof bosentan in phosphate buffer pH6.8

Drug Excipient Compatibility Study

FTIR Study

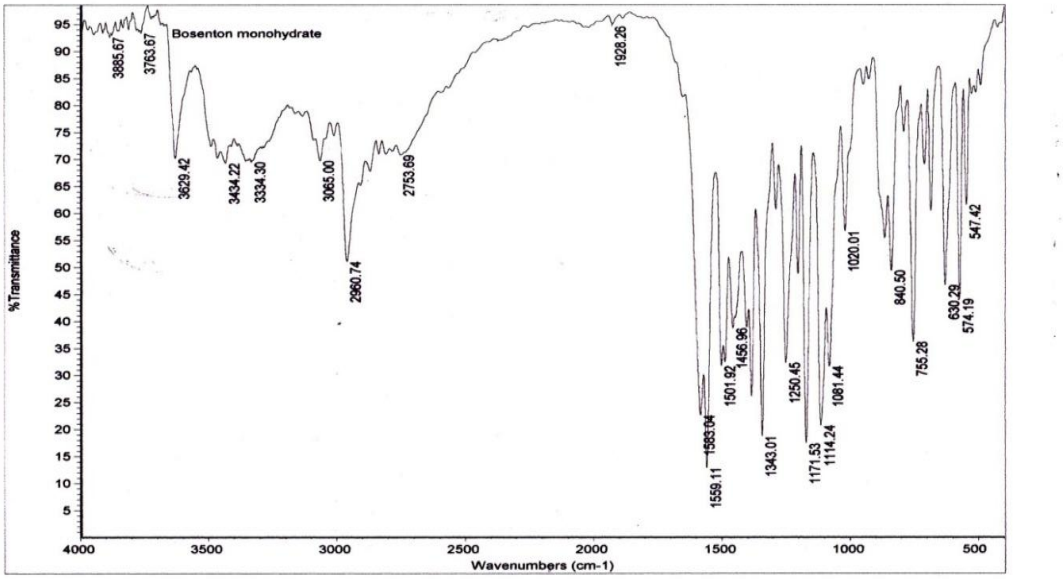

Fig no: 3 FTIR of Bosentan pure drug

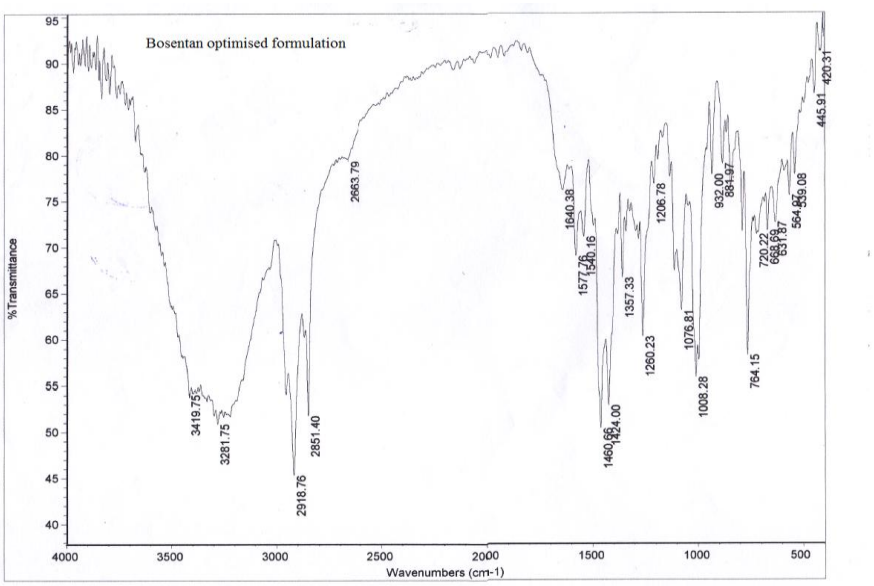

Fig no: 4 FTIR of bosentan optimized formulation

PRE-COMPRESSION PARAMETERS

Table no 7: 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	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
11	F10	0.49	0.57	14.04	28.58	1.16

Bulk density and tapped density

Bulk density and tapped density of powder blend was evaluated. The results were shown in the Table No 7 .Range from. 0.41 - 0.49

Angle of Repose

The angle of repose for the entire formulations blend was evaluated. The results were shown in the Table No 7 .Angle of repose of all the formulations ranges from .25.10 - 28.58.

Compressibility Index

Compressibility index for the entire formulations blend was evaluated. The results were shown in the Table No7 .Compressibility index of all the formulations ranges from.12.96 - 15.69

Hausner`s Ratio

The Hausner`s ratio for the entire formulations blend was evaluated. The results were shown in the Table No7. Hauner's ratio of all the formulations ranges from 1.15-1.19. All the pre-compression parameters were found to be within limits.

POST FORMULATION PARAMETERS

Table 8: Post formulation parameters of tablets containing Bosentan

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
F10	4.8	201	0.39	99.3

EVALUATION OF TABLETS

Hardness

The prepared tablets in all the formulations possessed good mechanical strength with sufficient hardness in the range of 4.8 to 5.9 kg/sq cm. Shown in table no.8

Friability

Friability values below 1% were an indication of good mechanical resistance of the tablets shown in the table no 8.

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 ten formulations was found to be 198 to 202 mg, which was in pharmacopoeial limits of ±5% of the average weight. Shown in table no.8

Drug Content

The percentage drug content of all the tablets was found to be around 99.8% of Bosentan which was within the acceptable limits. Shown in table no.8

DISSOLUTION STUDIES FOR OSMOTIC TABLETS

Table no 9: In-vitro drug release studies of osmotic tablets F_1 to F_{10}

Time in hrs	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
30 min	10.1	10.9	7.1	29.4	28.5	4.9	5.1	6.1	6.8	6.4
1	38.9	20.2	16.9	59.1	69.8	10.1	11.5	15.2	16.4	16.7
2	70.1	29.1	28.7	100.1	100.3	21.4	20.1	25.9	28.6	28.1
4	100.1	39.41	50.1	--	--	29.6	30.3	40.1	49.3	49.5
6	--	56.71	73.2	--	--	49.8	48.2	60.1	72.8	72.1
8	--	64.76	99.2	--	--	64.1	61.5	89.1	99.10	99.03
10	--	73.18	--	--	--	85.9	88.1	99.4	--	--
12	--	86.12	--	--	--	90.3	100.1		--	--

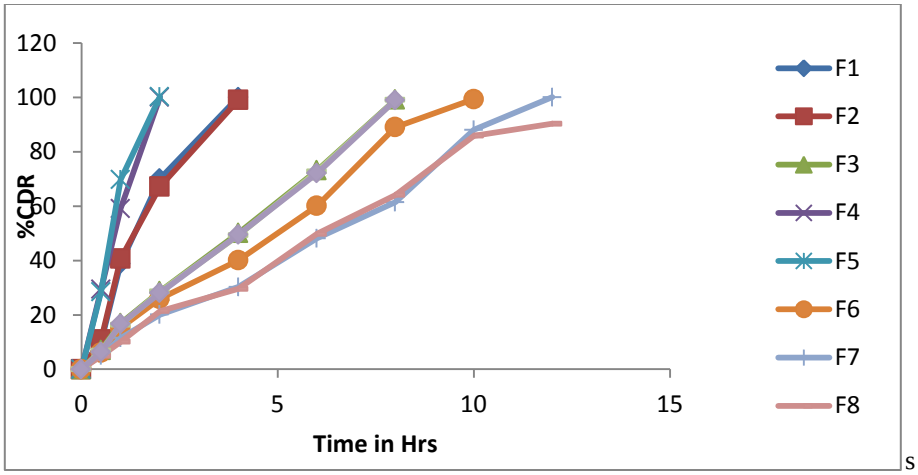

Fig no: 5 Dissolution graph for osmatic tabletics F1 to F10

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 due to the osmotic effect. Among all formulations F7 was optimized based on maximum drug release.

KINETIC STUDIES FOR OPTIMIZED FORMULATION (F7)

Table no 10: 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

CONCLUSION

The study was undertaken with an aim to formulate Bosentan as osmotic controlled release tablets. During this phase of investigation various factors that likely to affect the performance of the osmotic controlled release was studied. The release kinetics, dissolution rate, process variables such as hardness, weight variation are some of the factors found critical during the development based on the experimental findings. Preformulation studies were done initially and results directed the further course of formulation. With the literature review data, Preformulation and prototype formulation trails were started. Direct compression method was used for formulation. 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 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 Korsemeyer-peppas drug release kinetics model i.e super case 2 transports and non-Fickian model. 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 and it is less likely to be affected by various factors studied.

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