Research Article

FORMULATION AND EVALUATION OF BOSENTAN FLOATING MATRIX TABLETS

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ABSTRACT:

Bosentan is a dual endothelin receptor antagonist used in the treatment of pulmonary artery hypertension (PAH).in the present study Bosentan floating matrix tablets were developed to prolong the drug release and to retain the drug delivery system above the site of absorption for the desired period of time . The preformulation parameters such as flow properties and drug-excipient compatibility studies were performed. The results shown that all the polymers used in the study are compatible with the pure drug. The floating matrix tablets of Bosentan prepared by direct compression method and the tablets were evaluated for post compression parameters like average weight, thickness, hardness, friability and swelling index, floating lag time, total floating time and in-vitro drug release studies. SEM and stability studies were carried out only for best release formulation (F2). Among the nine formulations with PEO 301(F2) showed the maximum drug release upto 98% within 12 hrs. SEM for F2 formulation revealed that surface was smooth upto 4 hrs after that swelling and porosity of tablet increased indicating the diffusion and erosion mechanism of release.

Keywords: Bosentan, direct compression, floating matrix tablets, pulmonary artery hypertension.

INTRODUCTION

Over the past three decades, oral controlled release dosage forms have been extensively developed due to their various therapeutic advantages such as flexibility in formulation of dosage form, ease of administration and patient compliance. However, this approach suffers with few physiological hurdles such as inability to retain the dosage form within the desired region of the gastrointestinal tract due to variability in gastric motility and emptying rate[1]. Moreover, gastric emptying time in humans normally averages from 2 to 3 hrs[2] through the stomach and upper part of the intestine. Therefore brief gastric emptying time results in incomplete drug release from the drug delivery system which causes reduced efficacy of the administered dose[3]. However gastric emptying time is unpredictable and varies in individuals in case of any physiological problems and due to presence of food. Drugs with short half-life are quickly eliminated from the blood circulation and results in decreased bioavailability. This necessitated in controlled placement of a dosage form in a specific region of the GI tract which offers several advantages in administering drugs having narrow absorption window in the GIT or drugs having stability problem[4]. By following these considerations, oral controlled release dosage form with gastro retentive properties were developed. After oral administration, Gastro retentive dosage forms remain in the gastric region and prolong the gastric residence time of drugs for several hours. This enables the continuous drug supply at its absorption site in the upper gastrointestinal tract[5]. Prolonged gastric retention improves solubility of drugs that are less soluble, reduces drug waste, increase bioavailability and also suitable for local drug delivery to the stomach and proximal part of small intestine[6]. Once the drug gets released completely, the system is eliminated from the stomach. This results in better control of fluctuations in plasma drug concentrations. Various attempts have been made to develop controlled drug delivery system which provides therapeutically effective plasma drug levels for longer periods and also to reduce the dosing frequency and minimize fluctuations in plasma drug concentration at steady state by delivering drug in a controlled and reproducible manner.

Gastric retention enables to achieve increased bioavailability of new products with better therapeutic activity and patient compliance. Oral route of administration is known to be the best to achieve known pharmacokinetic and pharmacodynamic advantages for controlled drug delivery.

Gastro retentive dosage forms can be designed by the currently available techniques such as floating drug delivery system[7] bioadhesive or mucoadhesive systems[8, 9], expansion[10, 11], sedimentation[12,13] low-density systems[14,15,16], high density systems[17], raft systems incorporating alginate gels[18,19]

superporous hydrogels[20], magnetic systems[21], modified shape systems[22,23] and by the administering the pharmacological agents simultaneously which delay gastric emptying (atropine, Propentheline etc) or pharmaceutical excipients [24,25].

The floating drug delivery systems exhibit most of the characteristics of hydrophilic matrices and are known as 'hydrodynamically balanced systems' (HBS). When the polymer gets hydrated with the surrounding medium, a gel like barrier is formed at the outer surface; this enables them to maintain their low apparent density. The drug gets released from the swollen matrix formulation, as in case of conventional hydrophilic matrix forms. These matrix forms remain buoyant in the gastric fluid without affecting the intrinsic rate of emptying as their bulk density is lower than that of the gastric contents. Several studies have demonstrated the concept of buoyancy in terms of prolonged GRT of the floating forms, improved bioavailability of drugs and improved effects in clinical situations. The results obtained confirmed that presence of gastric contents allows the proper achievement of the buoyancy to the dosage form[26].

Advantages of Gastro Retentive Drug Delivery Systems

This site-specific drug delivery reduces undesirable side effects[27], minimize the fluctuation of drug concentrations and helps to obtain improved selectivity in receptor activation[28]. Drugs which degrade in colon, drugs having rapid absorption through GIT can be successfully formulated as FDDS. Bioavailability of drugs can be enhanced especially by retaining the drug at absorption site[29, 30].

Polyethylene oxide is used as a tablet binder at concentrations of 5–85%. The higher molecular weight grades of PEO can provide delayed drug release by the hydrophilic matrix approach [31]. Polyethylene oxide facilitates coarse extrusion for tableting [32] and is also used in hot-melt extrusion [33]. The relationship between swelling capacity and molecular weight enables its use in immediate as well as sustained-release matrix formulations. Polyethylene oxide can be radiation cross linked in solution to produce a hydrogel and can be used in wound care applications.

Bosentan is a dual endothelin receptor antagonist used in the treatment of pulmonary artery hypertension (PAH) to decrease the rate of clinical worsening in patients with WHO Class III or IV symptoms and to improve exercise ability. Endothelin-1 (ET-1) is a neurohormone and its effects are mediated by binding to ETA and ETB receptors present in the endothelium and vascular smooth muscle. Patients with pulmonary arterial hypertension have elevated levels of ET-1 concentrations in plasma and lung tissue. Bosentan acts as a specific and competitive antagonist of endothelin receptor types ETA and ETB. Bosentan has higher affinity for ETA receptors than for ETB receptors. Route of elimination of Bosentan is by biliary excretion followed by metabolism in the liver [34, 35, 36].

MATERIALS AND METHOD

MATERIALS

Bosentan was used as active ingredient. Different grades of polyethylene oxide like PEO 301, PEO coagulant and PEO 303 were used as the polymers. Sodium bicarbonate was used an effervescent agent. The other ingredients used were magnesium stearate, aerosil. All the materials used in experimental works were obtained from Ranbaxy Research Laboratories, Gurgaon, India. All reagents used were of analytical grade.

METHOD

Preparation of floating tablets of Bosentan

The composition of different formulation of Bosentan floating matrix tablets is shown in Table 1. All the floating matrix tablet formulations were prepared by direct compression method. Bosentan and all other ingredients were weighed separately and passed through sieve no:60 and blended for 15 minutes by using double cone blender. The powder blends were evaluated for flow properties such as angle of repose and compressibility index and their corresponding results were given. The powder blends lubricated with 0.5% magnesium sterate and directly compressed as matrix tablets.

Table 1: Formulation development of Bosentan floating matrix tablets

Ingredients (mg)	Formulation Table							
	F1	F2	F3	F4	F5	F6	F7	F8
Bosentan	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5
PEO 301	50	75	100	_	_	_	_	_
PEO 303	50	75	100	_	_	_	50	75
Sodium Bicarbonate	25	25	25	25	25	25	25	25
Aerosil	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Magnesium stearate	1	1	1	1	1	1	1	1
Total weight	143	168	193	143	168	193	143	168

EVALUATION OF PHYSICAL PARAMETERS

The physical parameters such as weight uniformity, hardness, friability and drug content were evaluated for the prepared matrix tablets as per the Indian pharmacopiel standards. The physical parameters results are given.

Table 2: Evaluation of bosentan floating matrix tablets

Formulation	Angle Of Repose	Compressibility Index(%)	Weight Uniformity(Mg)	Hardenss(Kg/Cm^2	Friability(%)	Drug Content(Mg/Tablet)
F-1	23.90	14.23	141+2.0	4.7+0.3	0.66	62.3+0.5
F-2	22.34	12.17	165+3.0	5.1+0.3	0.64	62.5+0.2
F-3	22.54	14.98	191+4.0	4.9+0.3	0.67	61.8+0.5
F-4	23.30	15.77	140+4.0	5.1+0.3	0.33	63.3+0.4
F-5	22.57	13.63	165+4.0	5.1+0.3	0.23	62.7+0.2
F-6	21.36	11.57	192+5.0	5.1+0.3	0.34	63.4+0.3
F-7	25.74	13.37	142+2.0	5.1+0.3	0.22	62.4+0.2
F-8	22.14	12.61	163+5.0	5.1+0.3	0.45	61.4+0.5
F-9	21.74	12.27	190+4.0	5.1+0.3	0.31	62.5+0.4

In- vitro dissolution studies

The release of Bosentan from floating matrix tablets (n = 3) was determined using USP dissolution testing apparatus type II (paddle method). The dissolution was performed using 900 ml of 0.1 N HCl medium, maintaining 37 ± 0.5°C temperature and 50 rpm. A 5ml sample of the solution was withdrawn from the dissolution apparatus at predetermined time intervals of 1 hr for 12 hours and the samples were replaced with prewarmed fresh dissolution medium. The samples were filtered through 0.45 µ membrane (nylon)and analysed by using HPLC method. Mobile phase consisting of phosphate buffer pH 7.4 and Acetonitrile was used in the 40:60 ratio. 250*4.6*5µ Inspire C18 column is used. Absorbance was measured at λ max 265 nm.

In- vitro buoyancy studies

Floating time was determined by using USPXXIII dissolution apparatus-II at 50 rpmusing 900ml of 0.1N Hcl and the temperature was mantainted at 37±0.5^{0}C, throughout the study.The duration of floating (floating time) is the time the tablet floats in the dissoution medium (excluding floating lag time, which is the time required for the tablet to raise to the surface) is measured by visual observation. The results were summarized.

Characterization

Based on the dissolution studies performed on all the formulations, some of the optimized formulations were selected for further investigations such as swelling index, DSC and SEM analysis.

Swelling index

The swelling behaviour of a dosage unit was measured by studying its weight gain. The swelling index of tablets determined by placing the tablets in the basket of dissolution apparatus using dissolution medium 0.1N Hcl at 37±0.5^{0}C.After 1,6 and 10 hrs each dissolution basket containing tablet was withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance. The experiment was performed in triplicate for each time point. Swelling index was calculated by using the following formula.

$$\text{Swelling index} = \frac{\text{Wet weight of tablet- Dry weight of tablet)}}{\text{Dry weight of tablet}}$$

Scanning electron microscopy

The scanning electron microscopy (SEM) analysis was conducted using jeol, Japan (Model-jsm 5610LV) for the optimized formulation, operated at an accelerated voltage of 15kv.

Differential scanning calorimetry

A differential scanning calorimeter (DSC 60, shimadzu) was used to obtain the DSC curves Bosentan floating matrix tablets prepared by direct compression method pepresenting the rate of heat uptake. About 10mg of sample was weighed in a standard open aluminium pans,were scanned from 20-300^{0}C, at a heating rate of 10^{0}C/minute while being purged with dry nitrogen.

Kinetic modelling of drug release

The mechanism of drug release from the floating tablets was analyzed by fitting the in vitro dissolution data of the formulations into the zero order, first order, Higuchi model and Korsmeyer- Peppas model as per the reported method.[40]

Accelerated stability studies

The accelerated stability studies were conducted for the optimized formulation (F-2) according to ICH guidelines. All formulations were sealed in aluminium packaging coated inside with polyethylene,, and samples were kept in humidity chamber at 40^{0}C and RH 75% for 6 months. At the end of the period samples were analyzed for drug content, floating characteristics, hardness values and in-vitro dissolution studies.

RESULTS AND DISCUSSION

Floating matrix tablet formulations were prepared as per the compositions shown in table 1. Before compression process the powder blends were evaluated for flow properties such as angle of repose and carr's index. The angle of repose and carr's index values for all the powder blends and they established good and free flowing characteristics. The flow property results are given in table 2.

All the batches of tablets were compressed under identical conditions to minimize processing variables. The compressed matrix tablets were further evaluated for physical parameters such as weight uniformity, hardness, friability and drug content. These studies revealed that all the tablet formulations were found to comply with the compendia requirements.ity and drug content of the prepared matrix tablets. The weight variations of prepared tablets were in the range of 140±4.0 to 192±5.0mg. The Hardness of the tablets ranged from 4.5 to 6 kg/cm^2 and friability ranged from 0.22% to 0.67% which ensure that the tablets withstand to the shocks of handling during its manufacturing, packaging and shipping. Drug content was found to be in the range of 97 to 101%. The physical parameters results are given in table 2.

Dissolution studies were preformed on all the tablet formulations by using USP paddle method (apparatus II). The drug release from the matrix tablets were extended upto 12 hrs in the formulations F-1 to F-3 containing PEO 301 at 35%,45% and 50% concentrations respectively as rate controlling polymer. The formulations F-4 to F-6 prepared by using PEO coagulant, failed to drug release up to 12 hrs. The formulations F-7 to F-9 containing PEO 303 as rate controlling poymer , has failed to drug release up to 12 hrs. Among all the formulations (F-1 to F-9) F-2 has shown 100% of drug release in 12 hrs. Hence F-2 was selected as optimized formulation.

All the floating matrix tablets formulations were found to be linear with first order release rate with R^2values in the range of 0.93-0.99. Thus the rate of drug release from all the matrix tablet formulations were concentration dependant and were linear with first order release rate constant (k_1).The higuchi costants for all the floating matrix tablets were in the range of 10-13(mg$^{1/2}$) indicating the controlled drug release from the dosage form. The amount of drug released v/s square root time plots were found to be linear with R^2 values in the range of 0.91-0.99. The drug release from the matrix tablet formulations were by diffusion process. The release exponent (n values) for all the matrix tablet formulations were in the range of 0.5-0.8 indicating that the drug release was by Non-fickian diffusion.

The formulations F-1 to f-9 floated with a floating lag time range of 12 to 22 seconds and continued to float throughout duration up to 12 hrs.

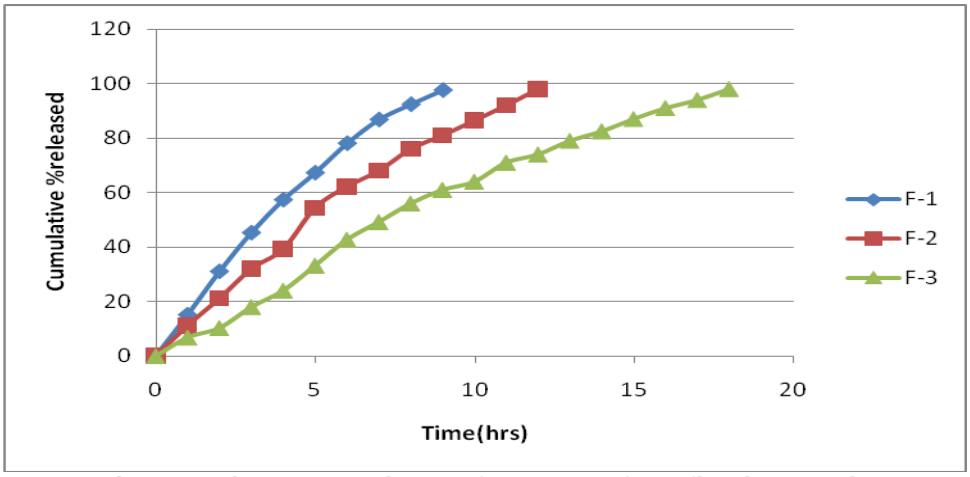

Fig. 1: In vitro Drug Release of Bosentan from floating matrix tablets prepared using PEO301

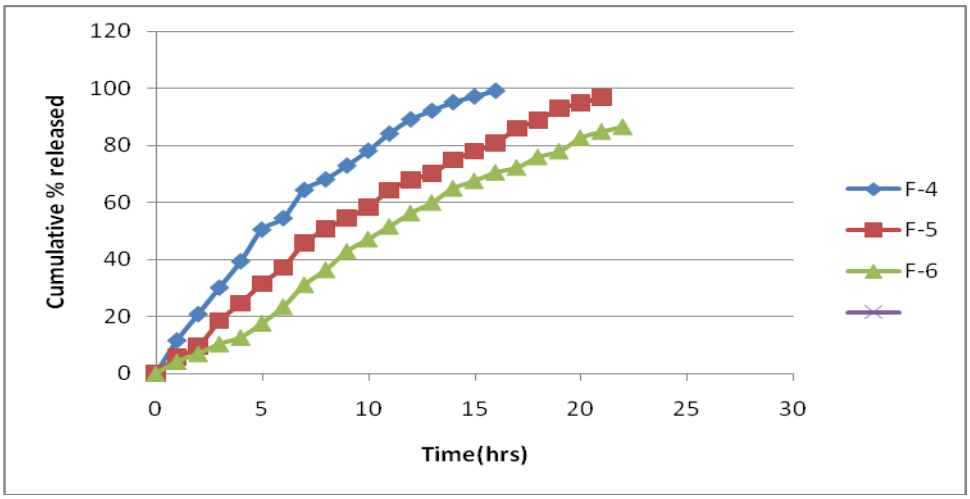

Fig. 2: In vitro Drug Release of Bosentan from floating matrix tablets prepared using PEO coagulant

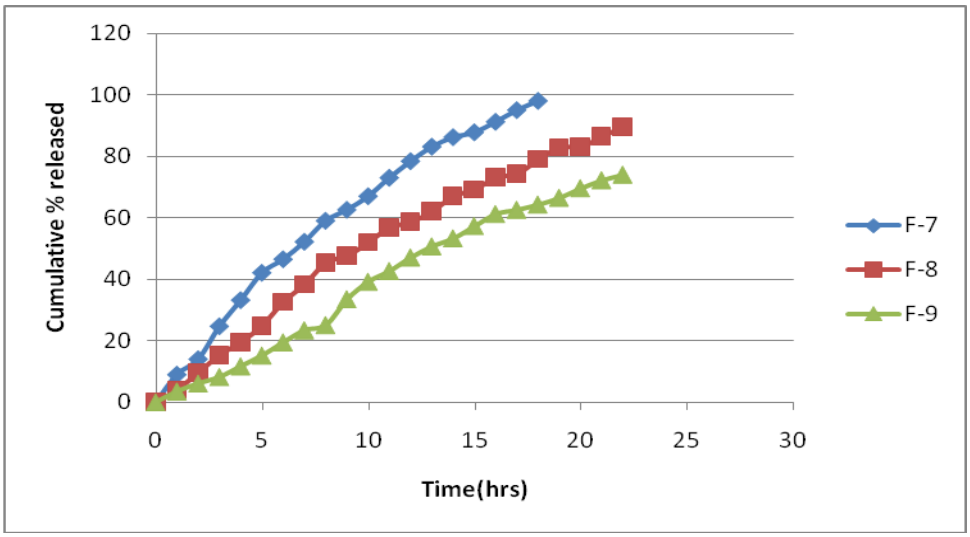

Fig. 3: In vitro Drug Release of Bosentan from floating matrix tablets prepared using PEO 303

Table 3: Floating charecteristics

Formulation code	Lag time(secs)	Floating duration(hrs)
F-1	14	17
F-2	16	17
F-3	12	18
F-4	15	16
F-5	16	22
F-6	15	24
F-7	22	18
F-8	17	24
F-9	16	24

Table 4: In vitro drug release profile

Formulation code	% drug released at 12 hrs
F-1	97.6
F-2	98
F-3	74
F-4	89
F-5	68
F-6	56.3
F-7	78.4
F-8	58.6
F-9	47.1

Table 5: Stability studies of optimized formulation F-2

Time	Hardness± S.D(kg/cm^2)	Drug content uniformity ±S.D(%)	%CDR
After 0 month	5.1±0.2	99.61±0.9	99.89
After 1 month	5.1±0.4	98.03±0.7	98.11
After 3 month	5.2±0.3	97.49±1.0	97.89
After 6 month	5.1±0.5	97.88±0.8	97.11

Table 6: Drug release profile of Bosentan floating matrix tablets

Formulation	First order		Higuchi		Peppas	
	K(hr^{-1})	R^2	K(mg$^{1/2}$)	R2	n value	R^2
F-1	0.2855	0.977	12.15	0.985	0.627	0.988
F-2	0.2634	0.990	11.94	0.978	0.666	0.967
F-3	0.5211	0.977	16.32	0.987	0.760	0.975
F-4	0.5423	0.996	17.06	0.991	0.794	0.987
F-5	0.2912	0.958	12.24	0.959	0.642	0.983
F-6	0.3254	0.978	12.66	0.987	0.605	0.983
F-7	0.3110	0.955	12.96	0.961	0.538	0.985
F-8	0.2990	0.974	12.25	0.977	0.750	0.987
F-9	0.3310	0.977	12.86	0.980	0.743	0.962

CONCLUSION

The release of drug from the tablet was influenced by the concentration of polymer used. It was observed that the drug release rate is reduced as the polymer concentration was increased. This may be due to the viscosity of the gel boundary at high polymer concentration which also indicates the effect of viscosity of different grades PEO used. As the viscosity is increased,, the drug diffusion length is increased and the drug diffusion coefficient is getting reduced. Hence the drug release is reduced. From the data formulations prepared with PEO 303 retarded the drug release at a better rate when compared to formulations prepared with PEO coagulant and PEO 301. It can be concluded that PEO can be used in appropriate concentrations to develop controlled release floating matrix tablets of Bosentan by incorporating appropriate concentration of sodium bicarbonate for gas generation.

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