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DEVELOPMENT AND EVALUATION OF BOSENTAN PULSINCAP FORMULATION FOR CONTROLLED RELEASE

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Abstract

A controlled release Pulsincap dosage form of Bosentan was developed for the treatment of pulmonary arterial hypertension (PAH), which lead to serious cardiovascular complications. Empty hard gelatin capsules were used to develop the Pulsincap formulations. Bodies of hard gelatin capsules were treated with formaldehyde for insolubility, and the caps of the gelatin capsules were used as such. The developed system contained hydrogel plug prepared with swellable polymer such as hydroxypropyl methyl cellulose (HPMC 10K), Guar Gum, Xanthan gum, and Sodium alginate together with pellets coated with drug and polymers separately at concentrations of 20, 30 and 40mg. Drug coating of Bosentan pellets was done by Fluid Bed Process Technology. All the formulations were assayed to determine drug content and the ability of the Pulsincap formulation to provide controlled release was assessed by in vitro drug release studies in buffer pH 1.2 for 2 hours, simulated intestinal fluid pH 7.4 for 3 hours and simulated colonic fluid pH 6.8 for 7 hours. The results indicated that significant drug release was obtained after 5 h from the start of experiment. Thus, Bosentan could be successfully delivered using developed Pulsincap formulation thereby reducing the systemic side effects.

Keywords: Bosentan; Pulsincap, HPMC 10K; Guar Gum, Xanthan Gum, Sodium Alginate.

Introduction

Many problems are associated with a conventional multiple-dosing regimen of long-acting therapy, such as systemic accumulation of the drug leading to side effects or toxicities, flip-flop profile of the plasma drug level, and poor patient compliance. The objectives identified as the outputs for addressing the identified development problem and provide a means to assess performance of controlled release formulation. The development of controlled release tablets had a clinical rational as it may reduce dose related side effects, improve efficacy and compliance to drug therapy. Controlled release products may be developed to reduce dose frequency, which adds to convenience

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of use, which in turn may facilitate compliance. Another rationale for developing controlled release preparation is smoothing the peaks of the plasma concentration curves (controlled release) in order to prevent peak concentration related adverse events [1].

Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, least aseptic constraints and flexibility in the design of the dosage form. It is well known that controlled release dosage forms may offer one or more advantages over immediate release formulations of same drug[2].

Hence, an attempt has been made on developing a controlled release Pulsincap dosage form of Bosentan for the treatment of pulmonary arterial hypertension (PAH), which lead to serious cardiovascular complications. Bosentan is an oral medication classified as an endothelin receptor antagonist (ERA) which is approved for the treatment of pulmonary arterial hypertension (PAH) in World Health Organization (WHO) Group 1 patients. Bosentan works by blocking endothelin, a substance made by the body[3]. Endothelin causes blood vessels to narrow (constrict). It also causes abnormal growth of the muscle in the walls of the blood vessels in the lungs. This narrowing increases the pressure required to push the blood through the lungs to get oxygen. By blocking the action of endothelin, causing vessels to relax, Bosentan decreases the pulmonary blood pressure to the heart and improves its function. This generally results in the ability to be more active. Research studies have verified this improvement[4].

Several pulsed release formulations have been developed recently. Tablet based or capsule based pulsatile formulation is the basis of the new drug delivery technology that addresses emerging trends and requirements[5, 6]. Assembly of the pulsed release capsule device consisted of swellable polymer weighed into the pre-coated capsule body, drug-coated pellets placed onto the compacted swellable polymer layer, an erodible plug made up of hydrophilic polymers inserted into the mouth of the capsule[7]. The capsule body is closed with water soluble cap. The effect of various parameters such as type and weight of swellable polymer, type of hydrophilic polymers used in erodible plug and weight of erodible plug was investigated in order to characterize the lag time, and the drug release profiles[8].

The main objective of the present study is to provide an improved oral controlled release by Pulsincap formulation at a therapeutic dose containing 62.5mg of Bosentan for 12 hours release useful for the treatment of hypertension and chronic heart failure[9].

Materials and methods

Materials

Bosentan was obtained from Alphamed formulations pvt ltd, Hyderabad as a gift sample. HPMC 10K was obtained from Drugs India, Hyderabad. Xanthan gum 80 mesh SR-2 and Guar gum 100 mesh, Sodium alginate food grades were purchased from SD fine Chemicals, Mumbai. All other ingredients, chemicals and solvents used were analytical reagent grade and were used as received.

Preformulation studies

Micromeritic properties

The angle of repose of Bosentan and formulation mixture was determined by the fixed funnel method. The bulk density and tapped density were determined by using a density apparatus. The Carr's index and Hausner's ratio were calculated[10, 11].

Compatibility studies

The compatibility of the drug in the formulation was confirmed by FTIR spectral analysis. FTIR spectra of pure drug, formulation containing all polymers were determined by using the Shimadzu FT-IR 8300 spectrophotometer by KBr pellet method in the wavelength region of 4000 to 400 cm^{-1}. The procedure consisted of dispersing a sample in KBr and compressing into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the light path, and the spectrum was obtained.

Methods

Preparation of core pellets

The composition of the pellets is given in Table 1. Non-pariel seeds (sugar pellets) (#22/#24) were procured from Aadhya Biotech Pvt. Ltd., Hyderabad. Due to high solubility, the sugar pellets immediately get dissolved in aqueous media. In order to retard the dissolution rate of non-pariel seeds initially coated with 2% (w/w) HPMC E5 as

a seal coat followed by coated with slurry of drug solution[12].

Coating procedure

The entire seal coating and drug layering processes were done by Fluid Bed Process Technology with the following specifications,

Inlet Temperature	: 38-40°C
Product Temperature	: 35-36°C
Exhaust Temperature	: 30-32°C
Atomization air pressure	: 1.2 bars
Peristaltic (Spray pump) speed	: 6-8 rpm
Fluidization air flow	: 50-60 cfm

Slurry of Bosentan with 6% Croscarmellose sodium, 1% povidone K-30 (w/w) and 0.01% tween 80 were dissolved in 100ml of acetone. The seal coated sugar pellets (Non-pariel seeds) (#22/#24) were preheated to about 35°C with gentle movement in FBD, and then sprayed the prepared slurry on to coating bed and % weight was build up to 30% w/w on sugar pellets while spraying the drug solution the pellets were allowed to suspended for about 10 min until uniform drug coating occurs. Spray rate, inlet air temperature were adjusted in such a way that the core bed reaches a temperature of about 35°C.

After sufficient amount of drug slurry was coated, the pellets were dried at about 45°C to have the moisture content of <2%. The dried pellets were sized using the sifter to remove agglomerates, broken pellets and fine powder [13].

Preparation of formaldehyde treated hard gelatin capsules

Empty hard gelatin capsules were used to develop the Pulsincap formulations. Bodies of hard gelatin capsules were treated with formaldehyde for insolubility, and the caps of the gelatin capsules were used as such. Bodies of hard gelatin capsules (Size 0) were placed on a wire mesh. Formaldehyde (15%) was taken into a petri dish and kept in a desiccator and potassium permanganate was added to it until vapors were produced. The wire mesh containing the bodies was then exposed to formaldehyde vapors. The reaction was carried out for 12 h after which the bodies were removed and dried at 50°C for 30 min to ensure completion of reaction between gelatin and formaldehyde vapors. The bodies were then dried at room temperature to ensure removal of residual formaldehyde[14].

Development of Pulsincap formulation

The developed system contained hydrogel plug prepared with swellable polymer such as hydroxypropyl methyl cellulose (HPMC 10K), Guar Gum, Xanthan gum, and Sodium alginate (SA 5 cps) together with pellets coated with drug and polymers separately at concentrations of 20, 30 and 40mg. Bodies of the gelatin capsule of size '0' hardened with formaldehyde for 12 hours were taken for preparing the Pulsincap body. 62.5mg equivalent weight of drug containing pellets were filled into the hardened capsule body. The remaining volume of the capsule body was filled with swellable polymer hydrogel plug and erodible plug. Then the soluble cap was locked into the body to form the controlled release Pulsincap device. The prepared Pulsincap devices were used for further evaluation studies[15].

Evaluation of pellets

Surface morphology of the pellets was studies using LEICA S440i scanning electron microscope after coating them with gold vapors. Morphological analysis was carried out at different magnification. The Carr's index and angle of repose of the pellets were also determined.

Evaluation of pulsincap

Disintegration test: 10 capsules with treated bodies and untreated caps were randomly selected. These capsules were then subjected to disintegration studies at room temperatures in buffers of pH 1.2, 7.4 and 6.8. A single capsule was placed in the buffer solution and stirred for 24 h. The time taken for the capsule to disintegrate was noted.

Uniformity of weight

20 Pulsincaps were randomly selected from each batch, weighed together and individually. The mean and standard deviation were determined.

Estimation of drug content

Ten Plusincaps were randomly selected, and the contents were removed and powdered. From this sample 100mg equivalent amount of drug containing powder was accurately weighed and transferred into a 100 ml volumetric flask. 10 ml of methanol was added to dissolve the content. The

solution is made up to the volume with pH 7.2 phosphate buffer. The resulted solution was filtered through 0.45µm filter paper and suitably diluted, and the drug content was estimated spectrophotometrically by measuring the absorbance at 270nm.

***In vitro* release study**

For *In vitro* release profile, dissolution studies were performed for 12h for designed Pulsincap dosage form according to USP dissolution apparatus I (Basket type) method. Acidic buffer pH 1.2 for 2 h, Phosphate buffer pH 7.4 for 3 h and Phosphate buffer pH 6.8 buffer for subsequent hours were used as dissolution media. The medium was rotated at 50rpm. Samples were withdrawn at specific time intervals and equal volume of media was replaced immediately. Withdrawn samples were then filtered, suitability diluted and the amount of drug released was determined by UV spectrophotometer at 270nm.

Table No. 01: Composition of Bosentan Pulsincap

Ingredients in mg/Pulsincap*	Bosentan equivalent to	HPMC K10	Guar Gum	Xanthan Gum	Sodium Alginate	Drug content
F1	62.5	10	--	--	--	100.12
F2	62.5	20	--	--	--	101.32
F3	62.5	30	--	--	--	100.49
F4	62.5	40	--	--	--	98.48
F5	62.5	--	10	--	--	102.47
F6	62.5	--	20	--	--	101.38
F7	62.5	--	30	--	--	99.62
F8	62.5	--	40	--	--	98.28
F9	62.5	--	--	10	--	101.47
F10	62.5	--	--	20	--	101.52
F11	62.5	--	--	30	--	100.48
F12	62.5	--	--	40	--	97.59
F13	62.5	--	--	--	10	98.28
F14	62.5	--	--	--	20	102.43
F15	62.5	--	--	--	30	101.48
F16	62.5	--	--	--	40	99.58

*All ingredients were taken in mg. All the formulations were assayed to determine the drug content.

Table No. 02: Pellet Analysis

Parameter	Observation
Appearance	Spherical with smooth surface
Average pellet size (mm)	0.94
Angle of repose (Θ)	23.59°
Bulk density (g/cc)	0.842
Tapped density (g/cc)	0.925
% Carr's Index	6.12

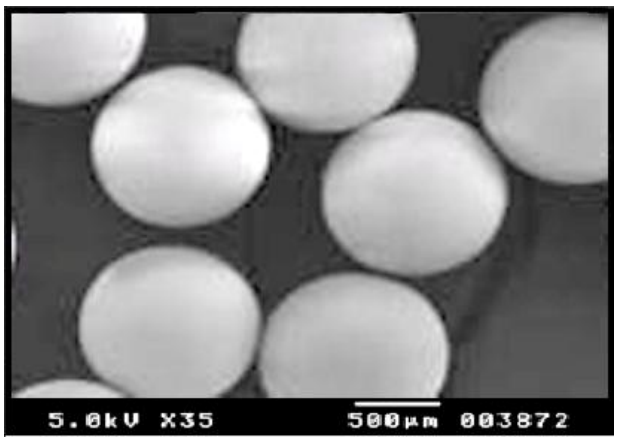

Fig. No. 01: SEM image of drug coated pellets

Results and discussion

The IR spectra of drug and polymer alone and prepared formulations shows no significant interaction between drug and polymer. The study confirmed the presence of all predominant peaks indicating its authenticity.

Surface morphology studies revealed that the pellets were discrete, spherical in shape and devoid of cracks (Figure 1). The pellets exhibited good flow properties as evident from Table. When the capsules were subjected to solubility studies in different buffers, the untreated caps disintegrated within 10 min in all the media whereas the treated bodies remained intact for about 24 h. The percentage drug content of the formulations was found to be between 96.12 to 102.07% of Bosentan, which was within the acceptable limits.

Developed Pulsincap formulations were subjected to preliminary *in vitro* release studies for a period of 12 h. Dissolution was carried out in three media such as simulated gastric fluid (acidic buffer pH 1.2) for the first 2 h, simulated intestinal fluid (phosphate buffer pH 7.4) for 3 h and simulated colonic fluid (phosphate buffer pH 6.8) for the subsequent hours. pH 7.4 and 6.8 were selected only to mimic the conditions in the small intestine and colon condition which were highly influenced in drug release mechanism.

The in vitro dissolution profiles of Pulsincap formulations during the 12 h study were shown in Figure. From the graphical representation it is revealed that the drug release from the Pulsincap has started roughly after 3 hours from the start of the experiment.

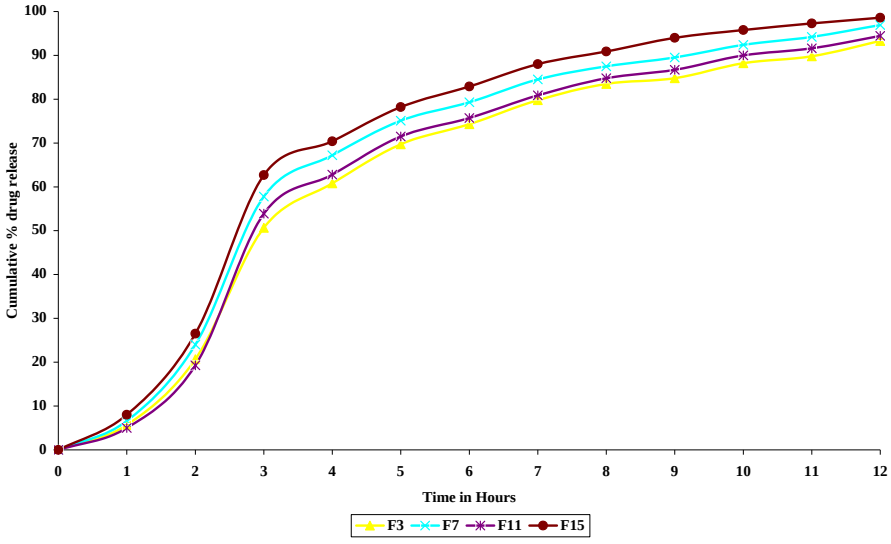

Fig. No. 02: In vitro release profile from F3, F7, F11 and F15

Conclusion

It was concluded that the release of Bosentan from the controlled release Pulsincap is proportional to the concentration of hydrogel. Formulation F3 (30 mg HPMC K10), F7 (30 mg Guar gum), F11 (30 mg Xanthan gum) and F15 (30 mg sodium alginate) are suitable for controlled delivery of Bosentan as they could minimize the drug release in the simulated gastric fluid and release major portion of the drug in the simulated small intestinal fluid, when compared to the other formulations. Among this batches, formulation F15 consists of hydrogel plug containing 30 mg of sodium alginate has shown better results, this formulation may fulfill the objectives. Therefore, the study proves that Bosentan can be successfully release in a controlled manner by use of developed Pulsincap formulation.

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