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DEVELOPMENT AND EVALUATION OF BOSENTAN PELLETS FOR PROLONGED DRUG RELEASE

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ABSTRACT

The present study was focused on preparation and evaluation of SR pellets of Bosentan. The preparation of extended release (ER), drug pellets of Bosentan were prepared by using fluid bed coating (FBC). These drug-loaded pellets were further coated with ethyl cellulose of two viscosity grades and Eudragit as rate controlling polymers, hypromellose as pore former and binder, acetyl tributyl citrate as plasticizer, and magnesium stearate as anti-adhering agent. The prepared pellets were evaluated for drug content, invitro dissolution, DSC, FT-IR and SEM. The prepared pellets were subjected for accelerated stability study. The drug release was extended up to 24 hours and the dreg release was mainly depends on the polymer type and polymer proportion. Accelerated stability showed good similarity with the initial formulation indicated good stability for 6 months. DSC and FTIR study showed the no drug polymer interaction. This technique can be showed good commercial success.

KEY WORDS

Bosentan, Pellets, EC, Eudragits, DSC and FT-IR.

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INTRODUCTION

Pellet drug delivery systems are the most widely accepted dosage form as they offer so many therapeutic benefits over single unit dosage forms like improved bioavailability because of larger surface area, reduced subjective variation and also pellets reduced chances of dose dumping. It is one of the most promising techniques for the multi particulate drug delivery systems[1]. The current study aimed on the palletized form of multiple units where the drug was loaded on the MCC spheres and further coatings were given to the drug to obtain prolonged drug release. These are oral dosage forms containing multi particulate discrete units, each revealing some desired characteristics [2-3]. Pellets provide a decrease in the dosage regimen and gastrointestinal irritation additionally controlling the drug release and increasing the absorption of the active ingredient and also reducing the dose dumping effect. The reproducibility of the release characteristics from pellet formulations is also much better with respect to the single-unit dosage forms. The pellets also resistance to the external factors such as moisture, air and light are the most advantageous properties of this dosage forms[4-7.] Bosentan is an endothelin receptor antagonist (ERAs). Patients with PAH have elevated levels of endothelin, a potent blood vessel constrictor, in their plasma and lung tissue. Bosentan blocks the binding of its receptors, there by negating endothelins deleterious effects. Its oral bioavailability is approximately 50% and food does not affect its absorption. It is having terminal elimination half-life of 5 hours [8].

MATERIALS AND METHODS

Bosentan was obtained as free sample from Aurobindo Pharma Ltd, Hyderabad. MCC spheres were obtained from Aurobindo Pharma, HPMC E5 was obtained from Colorcon Asia, Ethyl Cellulose, Eudragit of different grades and Magnesium stearate were obtained from Tini Pharma Pvt Ltd. All other chemicals and reagents used in the study were of analytical grade.

Preparation Methods:

Drug loading on MCC spheres:

MCC spheres were loaded in to the fluid bed processor[9-13], the process parameters were adjusted as per the machine setting. The MCC spheres then preheated to the required temperature as per the set parameters. The drug solution was then sprayed on to the spheres using peristaltic pump. The process parameters were monitored and then adjusted as per the pellets fluidization and weight gain. The prepared pellets were then dried for 12hrs in hot air oven to remove the complete moisture

ER coating solution on drug loaded pellets was prepared by using ethyl cellulose and eudragit. The solvent used in polymer solution was IPA and MDC. Tributyl citrate was used as plasticizer. Initially ethyl cellulose was added to the IPA and MDC 30:70 RATIO. The solution was then stirred for 30 min. then plasticizer was added to it finally talc and magnesium stearate was added and stirred to get the uniform dispersion. The prepared solution was sprayed on to the drug loaded pellets

Extended release coating on drug loaded pellets:

The drug loaded pellets were loaded in to fluid bed processor. The pellets were preheated up to 45^{0}C. The inlet and exhaust temperatures were set as per the requirement. The polymer solution was then sprayed on to the drug loaded pellets. Different ratio or percent of the polymer ethyl cellulose alone and in combination with eudragits were prepared and loaded on to the pellets. The pellets were then dried in a tray dryer overnight for complete evaporation of solvent.

Evaluation of extended release pellets: The prepared pellets were evaluated for various parameters such as drug content, *in vitro* dissolution, DSC, FTIR.

Drug content:

Drug content was estimated by spectrophotometric method at 272nm

***In vitro* dissolution studies**

Dissolution studies for each prepared formulation were performed in a calibrated dissolution test apparatus (LABINDIA), equipped with paddles (USP apparatus II method). 900ml of 0.1N HCL solution was used as a dissolution medium. The paddles were operated at 50 rpm and the temperature was maintained at 37± 0.5^{o}C throughout the experiment. Dissolution Samples were withdrawn from the apparatus at regular intervals i.e., 1, 2, 3up to 24hrs and replaced with equal volume of dissolution medium to maintain the sinc condition throughout the experiment. Samples were withdrawn at various time intervals were suitably diluted with same dissolution medium and the amount of drug released was estimated by chromatographically at 272nm.

Drug excipient compatibility studies:

To know the compatibility between drug and polymers used, compatibility studies were performed by using DSC and FTIR.

Thermal properties of pure drug were evaluated by Differential scanning caloriemetry (DSC) using Perkin Elmer. Accurately weighed 5-6 mg samples were hermetically sealed in aluminium pans and heated at a rate 5 ^{O}C/min from 50^{0}C to 250 ^{0}C temperature range under nitrogen flow of 25 ml/min.

FTIR spectra for pure drug, physical mixture and optimized formulations were recorded using a Fourier transform Infrared spectrophotometer. The analysis was carried out in Shimadzu-IR Affinity 1 Spectrophotometer.

The samples were dispersed in KBr and compressed into disc/pellet by application of pressure. The pellets were placed in the light path for recording the IR spectra. The scanning range was 400-4000 cm-1 and the resolution was 1 cm-1.

Scanning Electron Microscopy:

The surface morphology of prepared pellets was determined by scanning electron microscopy (SEM).

Stability studies:

Stability studies were carried out for the optimized batch according to the accelerated stability study. The dissolution profile after the stability study (graph 1) was similar compared to the samples soon after the preparation. The stability study of pellets was made for six months at 40 °C, 75% relative humidity (RH). The dissolution profile of pellets was found to be similar before the stability study. The testing of all the evaluation parameters related to the pellets were

performed (data not shown). Stability study results were compared, and it was found that there were no significant changes in the respective data before the stability study

RESULTS AND DISCUSSION:

In this present work, pellets of Bosentan were prepared by the fluid bed processor method. Initially core pellets were taken and were coated with the prepared coating solution of ethyl cellulose and eudragit individually and in combination.

Then the prepared pellets were evaluated for various physic- chemical properties, and all the formulations exhibited the properties within the limits. Then the formulations were observed for drug excipient incompatibility by studying DSC, FTIR studies, from these studies it was observed that there is no drug and excipient incompatibility as the thermo grams of pure drug and combination of drug and polymer showed similar endothermic peaks. From the SEM photographs it was observed that the shape of the prepared pellets was spherical, and coating was done completely.

In vitro dissolution studies were performed for all prepared pellets to find out the drug release, drug release mechanisms and also to know the effect of concentration and proportion of polymers used for extending the drug release from the core of the formulations. Among all the formulations CB12 formulation was selected as best or optimized formulation based on the drug release and its physical properties. The formulation CB12 was extended the drug release up to 24 hrs and it was prepared with ECN50 and eudragit polymer. The release kinetics showed that the drug release was followed ZERO order indicates the controlled drug release. The kinetics was best fitted to the Higuchi model and clearly indicates that the release mechanism was diffusion controlled.

The optimized formulation had shown similar properties after six months of stability studies i.e., in vitro drug release, drug content and physical appearance.

CONCLUSION:

An extrusion spheronization method was successfully applied to fabricate Bosentan prolonged-release pellets. Using scanning electron microscopy, it was shown that the Bosentan pellets were in a spherical shape. The *in vitro* release profiles indicated that the release of Bosentan from the pellets exhibited a controlled release behavior. DSC and FT-IR studies also showed the compatibility between drug and polymers. The stability studies also showed that the formulations had same physical properties and drug content and drug release after six months of study. The present work demonstrates the feasibility of controlled delivery of Bosentan utilizing MCC-based pellets.

ER Coating on MCC Spheres

Ingredients	**Mg/Unit**													
	CB1	**CB2**	**CB3**	**CB4**	**CB5**	**CB6**	**CB7**	**CB8**	**CB9**	**CB10**	**CB11**	**CB12**	**CB13**	**CB14**
Extended Release Coating on Drug loaded Pellets using EC N 10, N50 and Eudragit														
Drug Loaded Pellets	128	128	128	128	128	128	128	128	128	128	128	128	128	128
Ethyl Cellulose 10 cps	15	20	25	30	**	**	**	**	**	**	**	**	30	30
Ethyl Cellulose 50 cps	**	**	**	**	5	10	15	20	10	10	10	10	**	**
Eudragit NE30D	**	**	**	**	**	**	**	**	2.5	5	7.5	10	7.5	10
Talc	5	5	5	5	5	5	5	5	5	5	5	5	5	5
HPMC E 5	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Tributyl Citrate	2	2	2	4	4	4	6	6	6	8	8	8	8	8
IPA	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
MDC	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	**	**	**	**	**	**
Water									Qs	Qs	Qs	Qs	Qs	Qs
Th. Weight	156	161	166	168	146	151	158	163	157.5	162	164.5	167	184.5	187

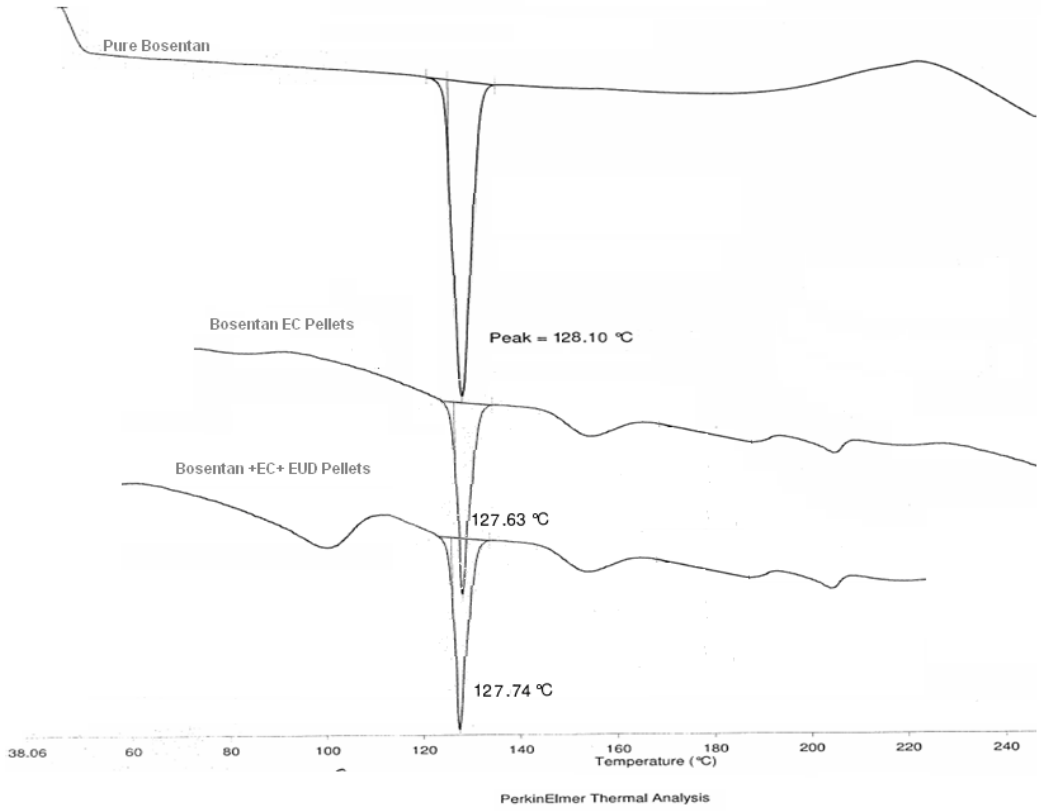


Figure 1: DSC thermogram of a) pure Bosentan b) physical mixture of Bosentan+EC c) physical mixture of Bosentan+EC+ eudragit

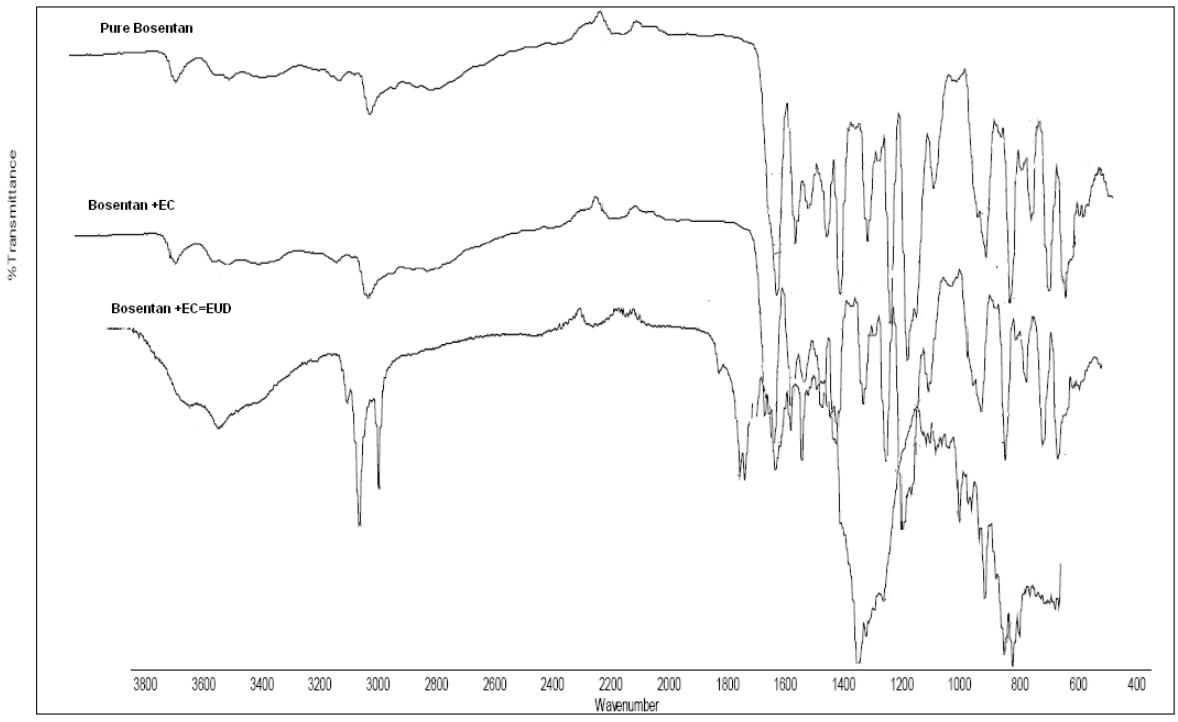


Figure 2: FT-IR spectrum of a) pure Bosentan b) physical mixture of Bosentan + EC c) physical mixture of Bosentan + EC + eudragit

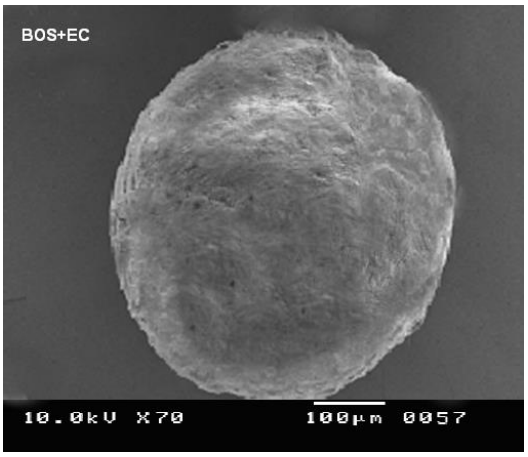


Figure 3: SEM of Bosentan pellet with EC

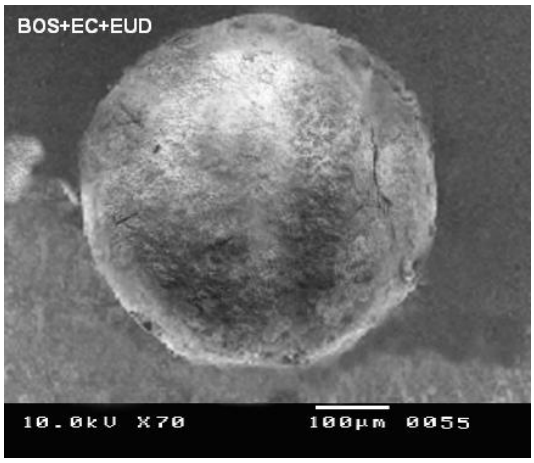
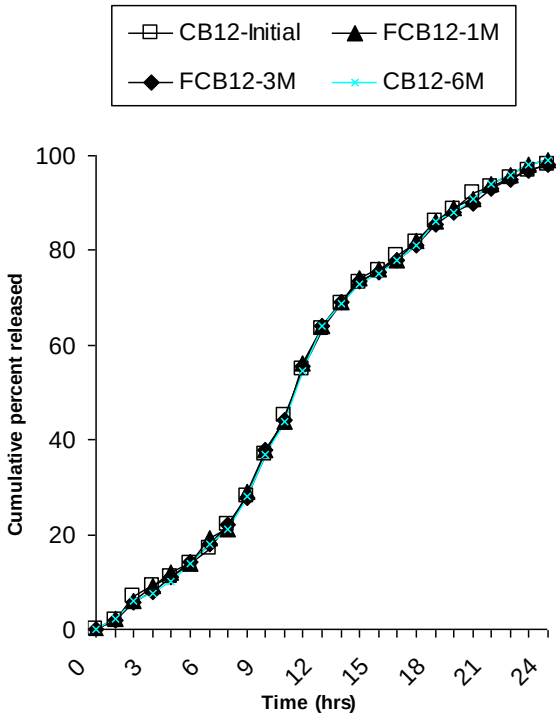


Figure 4: SEM of Bosentan pellet wth EC and Eudragit coating



Graph 1: *in vitro* drug release after 1 month, 3mnth and 6 months (stability studies)

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