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FORMULATION AND EVALUATION OF SUSTAINED RELEASE PELLETS OF BOSENTAN BY FLUIDIZED BED COATING PROCESS

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ABSTRACT
Multiparticulate drug delivery systems provide tremendous opportunities for designing new controlled and delayed release oral formulations. Multiparticulate dosage forms are gaining much favor over single-unit dosage forms in pharmaceutical applications. In the present investigation bosentan pellets were prepared for the sustained drug delivery for extended period of time. Bosentan is an antihypertensive drug having 50% of oral bioavailability. Bosentan sustained release pellets were prepared by using sugar pellets with EC as sustained release polymers, the pellet coating was performed by fluidized bed coating technique. The physicochemical characterization like SEM, DSC and *in vitro* dissolution studies were performed for all the formulations. It was found that among the various batches of formulations BEC-4 and BEC-5 were found to release the drug over an extended period of time, i.e. up to 18 hrs. As the concentration of the polymer increased the drug release from the pellet formulations was reduced. The sustained drug release profile has been maintained. So the present technique is successful in developing a sustained release pellet formulation for the bosentan.

KEYWORDS: Bosentan, pellets, Sustained release, ethyl cellulose, Fluidized bed Coating.

INTRODUCTION
Multiparticulate drug delivery systems are the utmost accepted and widely used dosage form as they offer so many benefits over unit dosage forms like improved bioavailability because of increased surface area, reduced inter subject variation and transportation and reduced chances of dose dumping. Pelletization is one of the most promising techniques for the multi particulate drug delivery systems.[1] The current investigation focuses on the pelletized form of multiple units where coating of sugar spheres with drug and further coatings were given to seal the drug and obtain sustain release, by a process pelletization which is stated to as a size widening process and the final product obtained is called pellets. The word 'pellet' has been used to define a variety of methodically produced, geometrically defined agglomerates attained from varied starting materials employing different processing conditions. These are oral dosage forms containing multiplicity of small 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. Also one of the beneficial properties of the pellet formulations is being a good candidate for the delivery of drug substances due to 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. They are suitable systems for film coating with respect to the low surface area- volume ratios. Also, resistance to the external factors such as moisture, air and light are the most advantageous properties of these dosage forms.[4,7]

In the current study, fluidized bed coater is employed for the preparation of bosentan pellets. A core material is coated with the drug substance using pan coater following a barrier coating process in which drug loaded pellets were coated with Ethyl cellulose using fluidized bed coater following a sustained release process in which the release controlling polymer material is introduced.[8,9] The coating process for pellets is carried out mainly in order to alter the release of drug from the pelletized drug delivery systems. The some of the coating equipment used for the pan coating processes are standard coating pan and the perforated coating pan.

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 endothelin's 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.[10,11]

The present research was mainly concentrated on the development and evaluation of sustained release pellets of bosentan with different concentrations of ethyl cellulose by employing fluidized bed coating technique.

MATERIALS AND METHODS

MATERIALS

Bosentan was obtained as gift sample from Dr. Reddy's laboratories, Hyderabad, India. Ethyl Cellulose, Cellulose diacetate, Povidone k-30, Acetyl tributyl citrate, Crosspovidone XL-10, Tween-80 were obtained as gift samples from Dow Chemical's Asia pvt. Ltd., Mumbai. Hypromellose phthalate, Talc, Isopropyl alcohol, Titanium dioxide, Acetone were obtained from Loba chemi Pvt. Ltd., Mumbai.

METHODS

Bosentan sustained release pellets were prepared by Direct Pelletization method using sugar pellets with EC and Cellulose diacetate as sustained release polymers, the pellet coating was performed by fluidized bed coating technique.

Equal quantities of bosentan and Crosspovidone XL-10 were taken in to bowl and mixed with hand. To the mixture another equivalent quantity of bosentan was added and mixed with help of hand then remaining quantity of drug was loaded in to the blender and mixed for 10 mins. Povidone solution was prepared by mixing povidone in isopropyl alcohol along with tween 80 for 10mins. The solution was filtered through nylon cloth into another container.

Non pareil seeds were loaded into the pan. On to the sugar pellets blends of bosentan and Crosspovidone XL-10 were loaded. Povidone solution was sprayed and pan was allowed to rotate for about 10 mins until uniform drug loading occurs. The drug loaded pellets from the pan were spread on to the trays uniformly and dried at 60°C temperature for about 3hrs. After drying the pellets were sifted by using vibro sifter to remove fines and collect the uniform sized pellets. The dried Drug loaded pellets were loaded into the coating pan to coat talc on the pellets while spraying remaining povidone solution. Agitate the bed to avoid lumps manually till the drug loading is completed and rotate the pan for 15 min. The talc loaded pellets from the pan were spread on to the trays uniformly and dried at 60°C temperature for about 2hrs. After drying, the pellets were sifted by using vibro sifter to remove fines and the uniform sized pellets were collected. The drug loaded pellets were charged in to fluidization basket. Cellulose diacetate polymer solution (Cellulose diacetate and povidone in IPA) was atomized on to the materials while the air is allowed to circulate into the basket to keep the materials under fluidized state. The process of fluidization was continued for 10 mins. The Cellulose diacetate coated pellets were charged in to fluidization basket. Polymer solution (hypromellose phthalate, titanium dioxide, acetone and isopropyl alcohol) was atomized on to the materials while the air is allowed to circulate into the basket to keep the materials under fluidized state. The process of fluidization was continued for 10 mins. The Hypromellose phthalate coated pellets were charged in to fluidization basket. EC Polymer solution (ethyl cellulose, Acetyl tributyl citrate, talc, IPA and acetone) was atomized on to the materials while the air is allowed to circulate into the basket to keep the materials under fluidized state. The process of fluidization was continued for 10 mins. The finally coated pellets were dried at ambient conditions for 2hrs and sifted through vibro sifter to collect uniform sized pellets. The composition of various bosentan sustained release pellets were given in Table 1.

Evaluation of sustained release pellets[12-14]

The pellets were evaluated for in process quality control tests. The following tests were performed for sustained release pellets.

Angle of repose

The angle of repose of bosentan pellets was determined by the funnel method (Repos gram). The accu-rately weighed quantity of pellets was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the pellets. The pellets were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$\tan \theta = h/r$

Where h and r are height and radius of the pellets cone, respectively. Flow properties for different values of an-gle of repose were given below.

Bulk density

Loose bulk density (LBD) and tapped bulk density (TBD) were determined. Bosentan was passed through a #18 sieve to break the clumps, if any. Accurately weighed 50 g of the drug was placed in a 100 ml graduated measuring cylinder. Initial volume was observed. The cylinder was tapped initially 500 times from a distance of 14 + 2 mm. The tapped volume (Va) was measured to the nearest graduated unit. The tapping was repeated additional 750 times. Again the tapped volume was measured to the nearest graduated unit. The LBD and TBD were calculated in g/ml using following formulae.

LBD = weight of the powder/volume of the packing

TBD = weight of the powder/tapped volume of the pack-ing

Content of active ingredients (assay)

The amount of active ingredient(s) present in drug coated pellets was determined. 421mg of pellets were accurately

weighed and placed in 100ml flask. The volume was made to 100ml using Distilled water containing 1%SLS. The flask was placed in sonicated for 10 mints. 1ml of the solution from the stock solution was pipette out into a 100ml volumetric flask. Volume was made up to 100ml with Distilled water containing 1%SLS. Out of this, 1ml was pipette out into a test tube and 9ml of Distilled water containing 1%SLS was added. Absorbance was measured at 272nm using UV. Percentage of drug present in the sample was calculated.

Friability test

Friability is the loss of weight of pellets in the container due to removal of fine particles from the surface. This in-process quality control test was performed to ensure the ability of pellets to withstand the shocks during process, handling, and transportation. Roche friabilator was used to measure the friability of tablets. It was rotated at 25rpm.

Particle size distribution

This practice was done for the pellets obtained after functional coating whether to check average size of the pellets. 100gms of the pellets are shifted in to a sieve shaker where a series of sieves was placed (16#, 22#, 25#, 30#). The machine was run for 5 mints, all the meshes are taken out and retained granules were collected by respective mesh and the percentage retention of pellets by that mesh was calculated.

***In vitro* dissolution studies**

Dissolution studies for each formulation were performed in a calibrated 8 station dissolution test apparatus (LABINDIA), equipped with paddles (USP apparatus II method) employing 900ml of distilled water as a medium. The paddles were operated at 50 rpm and the temperature was maintained at 37± 1^{o}C throughout the experiment. Samples were withdrawn at regular intervals up to 18 hrs and replaced with equal volume of dissolution medium to maintain the constant volume throughout the experiment. Samples withdrawn at various time intervals were suitably diluted with same dissolution medium and the amount of drug released was estimated by chromatographically at 272nm.

RESULTS AND DISCUSSION

The preformulation studies performed on Bosentan Fumarate and Bosentan along with excipient admixtures were found to be stable with no physical changes in the colour and amorphous nature. The drug content estimated in the admixtures by HPLC method was linear with the standard curve values. It was further confirmed that there was no interaction observed between drug and the polymers. DSC thermo graphic peak for Bosentan was observed at temperature 178.1oC. It was also observed that similar thermograph at same temperature with the drug and excipient mixture at 178.2oC was obtained. The preformulatory studies thus indicated that there were no drug and excipient incompatibilities. Based upon these studies suitable polymers were selected and Bosentan sustained release pellets were formulated.

Physical parameters of pellets

The % yield, Particle size and drug content of prepared pellets were found to be stable with the change in the concentration of polymer. % yield for all the pellets were in the range of 90-94.5% and the average particle size range of 1079 µ. The drug content in the all pellet formulations were in the range of 95-105%.

Dissolution Studies

Dissolution studies were performed on all the sustained release pellets by using U.S.P paddle method (apparatus II). The drug release from the pellet formulations were extended up to 18 hrs in majority of the formulations. BEC-1 formulation was failed to release the drug up to 18 hrs. Formulation BEC-1 extended the drug release up to 8 hrs where as the formulation BEC-2 extended the drug release up to 10hrs. The drug release rate decreases as the concentration of EC polymer composition increased. Among all the formulations BEC-3 and BEC-4 showed extended drug release i.e. > 90% at the end of 18hrs. The formulation BEC-5 showed very slow drug release (i.e. <85%) in 18hrs. It was observed that increase in the concentration of polymer Ethyl Cellulose resulted in delay in the drug release. The increase in the Cellulose diacetate polymeric concentration in formulations showed initial delay in drug release. Among the various batches of formulations BEC-4 and BEC-5 prepared by fluid bed coating were found to release the drug over an extended period of time, i.e. upto 18 hrs and meeting USP Bosentan Fumarate extended release test profiles once a day administration. The release exponent (n values) for all the pellet formulations were in the range of 0.45 to 0.8, indicated that the drug release was by non-Fickian diffusion. Thus the drug release from the pellet formulations was by diffusion of the drug from the polymeric matrix followed by erosion of the polymer. Thus mechanism of drug release from all the pellet formulations was by both polymer erosion and diffusion of the drug from the matrix systems.

SEM Analysis

SEM analysis was performed for the pellets prepared by fluid bed coating. The pellets prepared by FBC were having smooth surface with minimal pores indicated the uniform coating of the pellets.

DSC Analysis

DSC analysis was performed for the pure drug and pure drug with polymers. There was a characteristic endothermic peak (down) at 107.1^{o}C for the pure drug and temperature cycle is maintained at 20^{o}C/min. For the pure drug and the polymers, the DSC curve shows characteristic endothermic peak (up) at 107.2^{o}C and the temperature cycle was maintained at 50^{o}C /min. Thus both the DSC curves are exhibiting the characteristic endothermic peak at the same temperature which infers

that there is no interaction between the drug and the polymers used.

Table 1: Composition of Various bosentan Pellets Prepared By Fluid Bed Coating Method.

Ingredients for 10gms	EC-1	EC-2	EC-3	EC-4	EC-5
Bosentan	5	5	5	5	5
Povidone K-30	0.275	0.275	0.275	0.275	0.275
Ethyl Cellulose	0.010	0.012	0.014	0.016	0.018
Cellulose diacetate	0.014	0.014	0.014	0.014	0.014
Hypromellose	0.135	0.135	0.135	0.135	0.135
Titanium dioxide	0.015	0.015	0.015	0.015	0.015
Acetyl tributyl citrate	0.01	0.01	0.01	0.01	0.01
Acetone	2.308	2.308	2.308	2.308	2.308
IPA	5	5	5	5	5
Talc	0.037	0.037	0.037	0.037	0.037
Crosspovidone XL-10	0.06	0.06	0.06	0.06	0.06
Non paerile seeds	4.420	4.418	4.416	4.414	4.412
Purified Water	1.84	1.84	1.84	1.84	1.84
Tween-80	0.024	0.024	0.024	0.024	0.024

Table 2: Micromeritic characterization of bosentan pellets formulated by FBC.

S. No	Formulations	BD	TD	CI	HR	Bulkiness
1	BEC-1	0.397	0.443	10.384	1.116	2.519
2	BEC-2	0.386	0.431	10.441	1.117	2.591
3	BEC-3	0.381	0.426	10.563	1.118	2.625
4	BEC-4	0.379	0.422	10.190	1.113	2.639
5	BEC-5	0.376	0.42	10.476	1.117	2.660

Table 3: Physical parameters of bosentan pellets formulated by FBC.

S. No	Formulations	%Yield ± SD	Particle Size ± SD (µ)	% Drug Loading ± SD
1	BEC-1	91.5 ± 0.2	1072 ± 20	98.2 ± 0.3
2	BEC-2	92.6 ± 0.6	1063 ± 25	97.6 ± 0.6
3	BEC-3	91.6 ± 0.5	1069 ± 16	99.5 ± 0.4
4	BEC-4	93.9 ± 0.2	1061 ± 24	101.9 ± 0.2
5	BEC-5	90.2 ± 0.2	1082 ± 34	98.0 ± 0.5

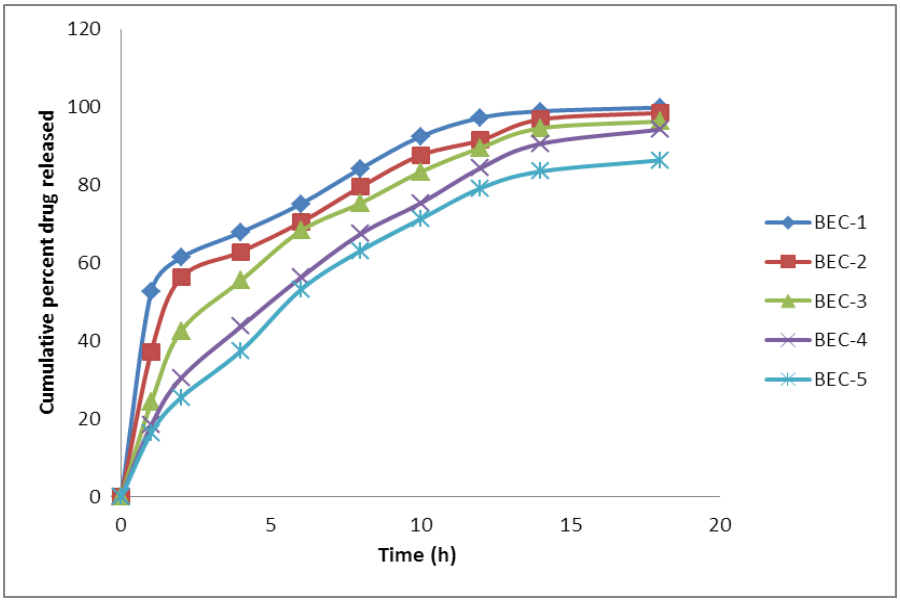

Figure 6.29: Drug release profile of bosentan pellets formulated by FBC.

Table 4: Drug release kinetic parameters of bosentan pellets formulated by FBC.

Formulation	Zero Order		First Order		Higuchi	PEPPAS	
	k	r^2	k	r^2	r^2	k	n
BEC-1	4.135	0.911	0.200	0.675	0.888	0.971	0.49
BEC-2	4.465	0.953	0.188	0.758	0.942	0.970	0.57
BEC-3	4.921	0.985	0.181	0.835	0.978	0.971	0.63
BEC-4	5.134	0.986	0.158	0.912	0.980	0.993	0.77
BEC-5	5.134	0.908	0.115	0.895	0.985	0.990	0.81

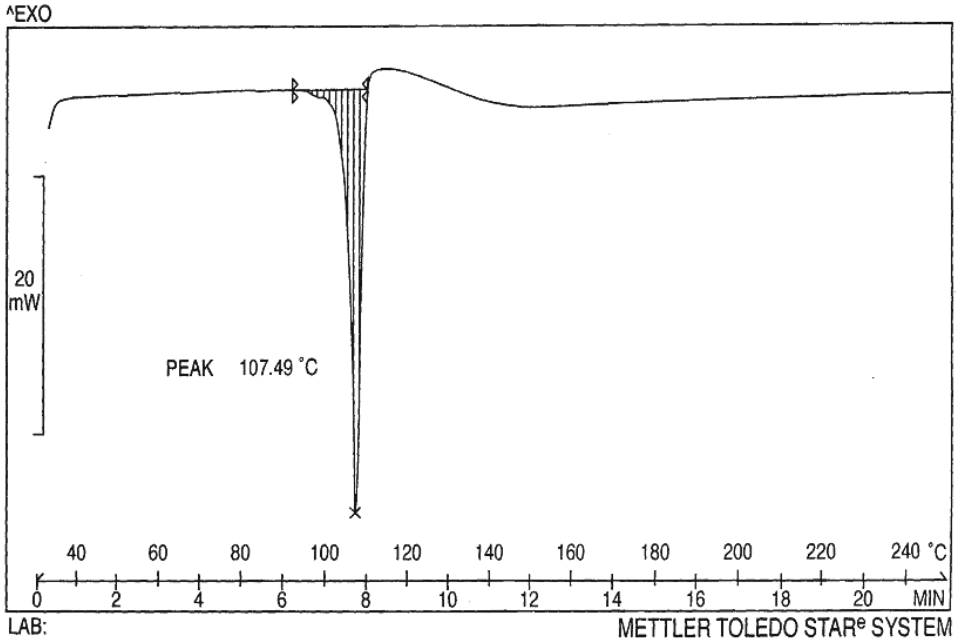

Figure 2: DSC thermogram of bosentan.

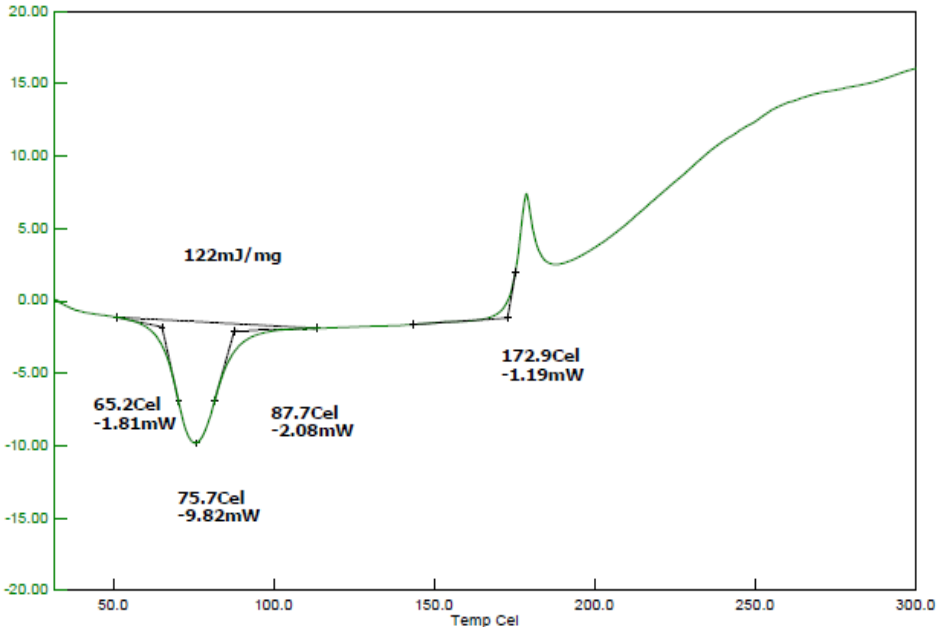

Figure 3: DSC thermogram of Ethyl cellulose.

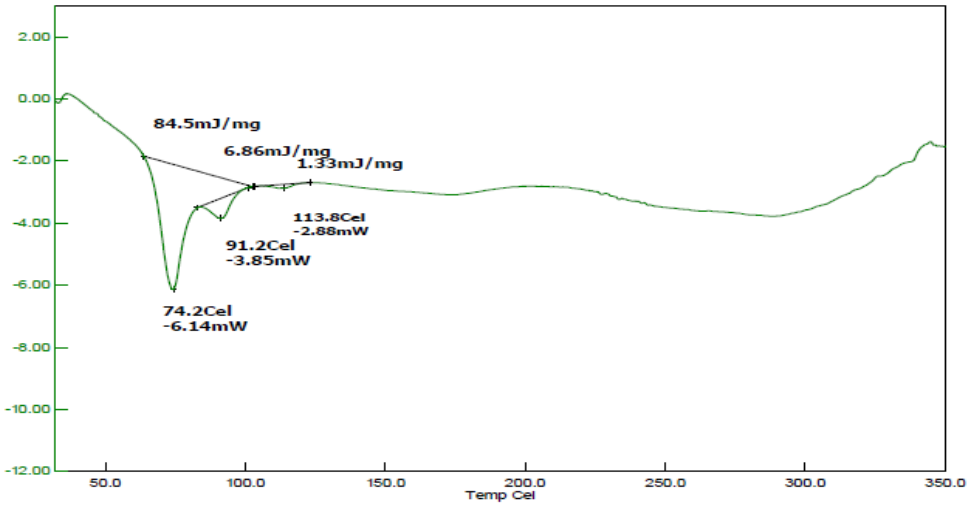

Figure 4: DSC thermogram of Drug+Ethyl cellulose.

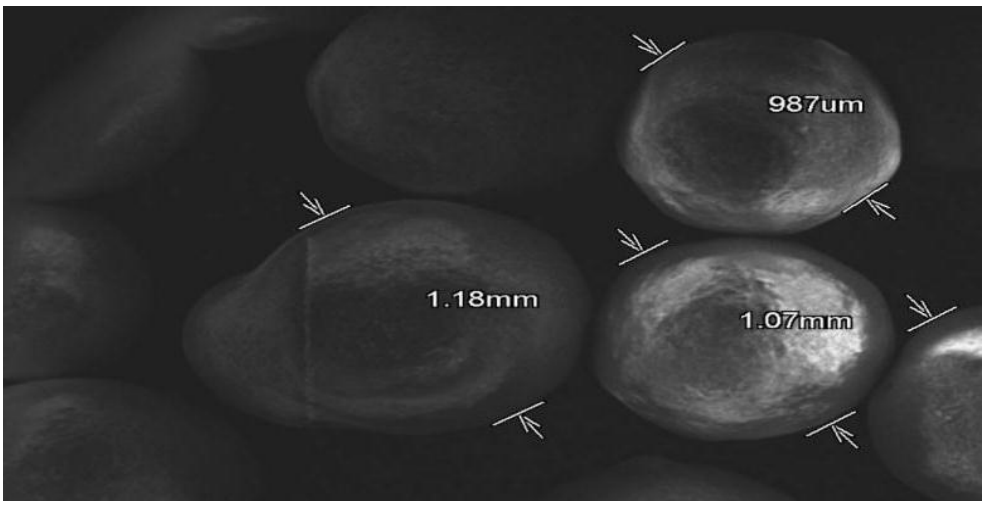

Figure 5: SEM image of BEC-4 formulation.

CONCLUSION

The Bosentan sustained release pellets were prepared by fluidized bed coating process. Ten formulations were prepared by using EC and Cellulose diacetate polymers as release retardants. The polymers chosen showed no significant interaction with drug which was evident from DSC studies. The physicochemical characterization of pellets was studied by SEM analysis. The i*n vitro* dissolution studies have been performed for all the formulations. Good correlation and reproducible results were obtained with formulations EC-4 and EC-5 thus showing good *in-vitro* dissolution profile. As the concentration of the polymer increased the drug release from the pellet formulations was reduced. The sustained drug release profile has been maintained. So the present technique is successful in developing a sustained release pellet formulation for the Bosentan.

Recommendations

The scalability of multiparticulate systems facilitates the formulation of these type of dosage forms more easy for industrialists. The advantages of uniformity in size and shape avoids the weight variation and drug dissolution problems when compared to single unit dosage forms such as tablets or capsules. Formulation of Bosentan pellets for sustained drug release can be adopted in large scale. With the advantage of requirement of small polymer concentrations to get sufficient sustained effect, one can drastically reduce bio burden of polymers and eventually their relative side effects. Due to requirement of small polymer quantities the formulations can also be cost effective.

REFERENCES

1. V.V.N. Haritha; Multiparticulate Drug Delivery System; Pelletization; American Journal Of Pharma Tech Research, 2012; Pg 82-87.
2. NS Dey et al: Multiparticulate Drug Delivery Systems For Controlled Release; Tropical Journal Of Pharmaceutical Research, September 2008; 7(3): 1067-1075.
3. Shailesh L et al.,: Controlled Release Approach To Novel Multiparticulate Drug Delivery System; International Journal Of Pharmacy and Pharmaceutical Sciences, 2012; 4(3): 757-763.

4. Mangesh E. Bhad et al.,; MUPS Tablets-A brief Review; International Journal Of Pharm Tech Research, 2(1): 847-855.
5. Hiren P.Patel et al.,; Pellets: A General Overview; International Journal Of Pharma World Research, 2010; 1(2): 1-15.
6. Kammilli Lavanya et al.,; Pelletization Technology: A Quick Review; International Journal Of Pharmaceutical Sciences and Research, 2011; 2(6): 1337-1355.
7. Vikash Dash et al.,; Pelletization Technique In Drug Delivery System; Journal Of Current Pharmaceutical Research, 2012; 9(1): 19-25.
8. Strübing et al. Characterization of poly (vinyl acetate) based floating matrix tablets, Journal of Controlled Release, 2008; 12: 149–155.
9. Y.S.R. Krishnaiah et al. A three-layer guar gum matrix tablet for oral controlled delivery of highly soluble metoprolol tartrate. International Journal of Pharmaceutics, 2002; 241: 353–366.
10. Holm P, Liska J, Clozel Ml. The endothelin antagonist bosentan: hemodynamic effects during normoxia and hypoxic pulmonary hypertension in pigs. J Thorac Cardiovasc Surg, 1996; 112: 890–897.
11. Provencher S, Sitbon O, Humbert M. Long-term outcome with first-line bosentan therapy in idiopathic pulmonary arterial hypertension. Eur Heart J, 2006; 27: 589–595.
12. X. Wei et al. Sigmoidal release of Indomethacin from pectin matrix tablets: Effect of in situ cross linking by calcium cations. International Jour-nal of Pharmaceutics, 2006; 318: 132–138.
13. Ishida et al. A novel approach to sustained pseudoephedrine release: Differentially coated mini-tablets in HPMC capsules. International Journal of Pharmaceutics, 2008; 359: 46–52.
14. Chavan S, Anantwar S. Design and evaluation of once daily sustained release matrix tablets of Nicorandil. International Journal of Pharmacy and Pharmaceutical Sciences, 2011; 3(2): 13-18.