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SUSTAINED RELEASE PELLETS OF BOSENTAN FORMULATION AND BIOPHARMACEUTICAL EVALUATION

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ABSTRACT
Designing novel controlled and delayed release oral formulations is made possible by multiparticulate drug delivery technologies. In pharmaceutical applications, multiparticulate dosage forms are becoming more and more popular than single-unit dosage forms. In the current study, bosentan pellets were made for the ongoing medication administration for a long time. The oral bioavailability of the antihypertensive medication bosentan is 50%. Sugar pellets containing EC as sustained release polymers were used to create bosentan sustained release pellets, and the fluidized bed coating process was used to coat the pellets. For every formulation, physicochemical characterizations such as SEM, DSC, and in vitro dissolution experiments were carried out. Among the several formulation batches, it was discovered that BEC-4 and BEC-5 released the medication for a longer duration—up to 18 hours. The drug release from the polymer increased as its concentration rose. The number of pellet formulations was decreased. The profile of persistent drug release has been preserved. Thus, the current method is effective in creating a bosentan sustained release pellet formulation.

KEYWORDS: Bosentan, pellets, Sustained release, ethyl cellulose, formulations, Coating.

1. 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. A range of carefully created, geometrically defined agglomerates have been referred to as "pellets." from a variety of raw materials using various processing settings. These oral dosage forms come in a variety of tiny, distinct units, each of which exhibits a few desired properties.[2,3] In addition to reducing gastrointestinal discomfort and dose requirements, pellets also regulate medication release and improve active component absorption. Another advantage of pellet formulations is that they are an excellent option for medication administration since they lessen the effect of dosage dumping. Additionally, the repeatability of the release properties from pellet formulations is significantly superior than the dosage forms in single units. Because of their low surface area-to-volume ratios, they are appropriate systems for film coating. The most beneficial characteristics of these dose forms are also their resistance to environmental elements including moisture, air, and light.[4,7]

The bosentan pellets used in this investigation are prepared using a fluidized bed coater. Pan coater is used to apply the medicinal ingredient to a core material. after a sustained release procedure where the release-controlling polymer material is injected, and after a barrier coating procedure where drug-loaded pellets were coated with ethyl cellulose utilizing a fluidized bed coater.[8,9] The primary purpose of the pellet coating procedure is to modify the medication release from the pelletized drug delivery devices. Standard coating pans and perforated coating pans are two types of coating equipment used in pan coating procedures.

Bosentan is an antagonist of the endothelin receptor (ERA). Endothelin, a strong blood vessel constrictor, is

found in higher concentrations in the plasma and lungs of patients with PAH. tissue. Bosentan eliminates the harmful effects of endothelin by preventing its receptors from binding. Food has little effect on its absorption, and its oral bioavailability is around 50%. It has a five-hour terminal elimination half-life.[10,11] The creation and assessment of bosentan sustained release pellets with varying ethyl concentrations was the primary focus of this study. Cellulose with the use of the fluidized bed coating method.

2. MATERIAL AND METHODS

2.1 DESIGN AND CHARACTERISATION OF BOSENTAN PELLETS

Ethyl cellulose was used as a polymer in the fluidized bed coating method to create bosentan pellets, which had a 12-hour sustained release. Acetyl tributyl citrate was employed as a plasticizer in this procedure, while isopropyl alcohol and acetone served as solvents. For fluidized bed coating, the loading and maintenance dosages determined in Sec. 3.1 were also utilized to achieve the intended release rate for up to 12 hours with zero order release.

2.2 Preparation of bosentan drug loaded pellets

Table 1 lists the chemicals that were used to prepare the drug-loaded pellets. In the fluidized bed coater's chamber, 200 g of Nonpareil seeds were first taken (Umang coater, Wurster Insert, Umang Ltd, Mumbai, India). Bosentan 74 g Using a paddle stirrer, 200 mL of isopropyl alcohol-acetone (1:1) was continuously stirred at 100 rpm to dissolve g of povidone K-30 as a binder. Using the bottom spray mode and the solution layering approach, this medication solution was fully sprayed onto Nonpareil seeds.[12] To prevent lumps at sporadic stages, talc was manually added to drug-loaded pellets (4 g).

Table 1: Composition of drug loaded Pallets.

Ingredients	FC1	FC2	FC3	FC4	FC5	FC6	FC7	FC8	FC9
Bosentan(mg)	74	74	74	74	74	74	74	74	74
Nonpareilseeds (mg)	200	200	200	200	200	200	200	200	200
PovidoneK-30 (mg)	22	22	22	22	22	22	22	22	22
Isopropylalcohol-acetone(mL)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Talc(mg)	4	4	4	4	4	4	4	4	4
Totalweight (mg)	300	300	300	300	300	300	300	300	300

2.3 Polymer coating of drug loaded pellets

300 g of drug loaded pellets were charged into fluidization chamber (Umang coater, Wurster Insert, Umang Ltd., Mumbai, India). Ethyl cellulose polymer solution was atomized on the pellets through bottom spray using the optimized process parameters.[13] The weight gain in the coating of the pellets was determined intermittently and coating was stopped after reaching the required percent weight gain. The coated pellets were dried under fluidization state for 2 hours and coated pellets were sifted through sieve no. 20/25 using vibro sifter. Different batches of coated drug loaded pellets were prepared and the composition of percentage weight gain in coating pellets is shown in Table 2.

Table 2: Composition of polymer coated pellets.

Ingredients	FC1	FC2	FC3	FC4	FC5	FC6	FC7	FC8	FC9
Drug loaded pellets (mg) containing 74 mg of drug	300	300	300	300	300	300	300	300	300
Weight of coat applied (%)	5	7.5	10	12.5	15	17.5	20	22.5	25
Total weight gain (mg)	315	322.5	330	337.5	345	352.5	360	367.5	375

3. Evaluation of polymer coated pellets

The pellets were evaluated for the percent yield, % drug content, moisture content, angle of repose, bulk density, tapped density, friability, particle size analysis and subjected to in vitro drug release studies and drug release mechanisms as per the procedure described in Sec.3.3

3.1. Percentage yield

Percentage yield of coated pellets was in the range of 90-97%. Among them FC6 had achieved highest yield 97% and FC2 had achieved lowest yield 90.32% which indicated that every formulation has received satisfactory level of coating. The results are represented in Table 3.

3.2 Estimation of percent drug content

Drug content of pellet formulations (PC1-PC6) was found to be 87.51 to 98.97% which revealed that the drug content was within the limits prescribed by I.P. Drug content of all formulations is shown in Table 3.

3.3 Percentage moisture content

The obtained results of percent moisture content for different batches are depicted in Table 3. Percentage moisture content values for all the prepared coated pellets were found to be in the range of 2.11% to 2.42%. From the results, no significant percentage moisture content was observed.

3.4 Micromeritic properties

The results of angle of repose, bulk density and tapped density are shown in Table 3. The bulk density, tapped density for all the formulations were found to beless than 1 g/cm3. The angle of repose values were in the range of 9.44° to 11.22°. The results of the micromeritic properties indicated excellent flow properties for pellets, which may be due to the spherical shape of the pellets.

3.5 Friability study

The results of friability study are presented in Table 3. The percentage weight loss in the friability test was found to be less than 1% for the all the formulated batches, which indicated that the ability of the pellets to withstand abrasion in packing, handling and shipping.

3.6 Particle size determination

According to experimental findings average particle size was 837 µm. Overall 90% of the pellets were obtained in the desired particle size range proving that the process is very reproducible for all the batches of coated pellets. There was no agglomeration of particles. The results are shown in Figures 1 and 2.

Table 3: Evaluation parameters of bosentan pellets (mean ± s.d., n=3).

Batch	%Yield	%Drug content	Moisture content (%)	Angle of repose(°)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Friability (%)
PC1	92.78±0.32	87.51±0.25	2.21±0.12	10.18±0.06	0.78±0.015	0.80±0.025	0.04
PC2	93.71±0.21	90.97±0.14	2.11±0.21	10.38±0.12	0.71±0.009	0.86±0.091	0.05
PC3	93.79±0.22	89.94±0.11	2.42±0.14	11.22±0.14	0.79±0.004	0.86±0.004	0.03
PC4	94.81±0.15	98.97±0.24	2.19±0.11	09.44±0.21	0.81±0.023	0.81±0.011	0.03
PC5	91.71±0.64	92.05±0.14	2.37±0.15	09.54±0.13	0.79±0.004	0.88±0.012	0.04
PC6	93.73±0.35	91.86±0.14	2.19±0.13	10.18±0.11	0.73±0.022	0.84±0.022	0.05

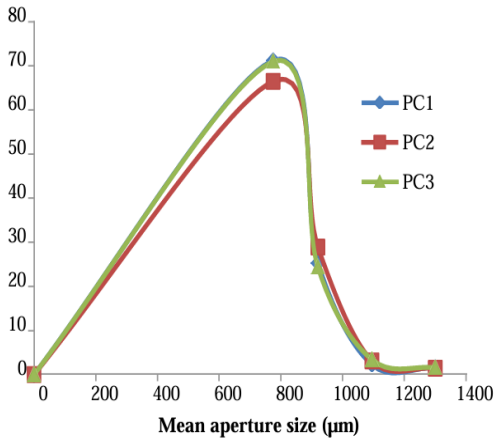

Figure 1: Particle size distribution of PC1-PC3.

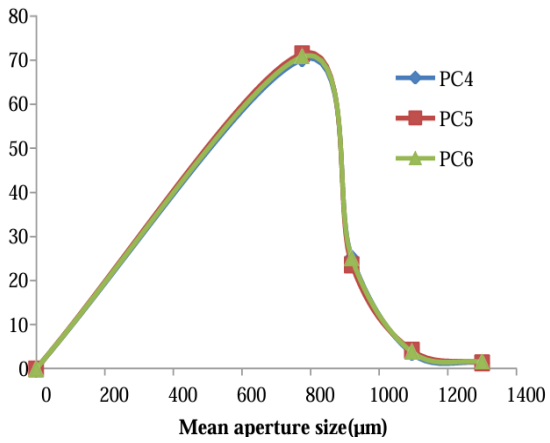

Figure 2: Particle size distribution of PC4-PC6.

4. IN VITRO DISSOLUTION STUDIES

Drug layered pellets were subjected to dissolution and 100% of drug was released within 3 hours. Dissolution of immediate release commercial tablet, Bosentas 62.5 was also conducted to compare the release of bosentan with that of coated pellets and the results are shown in Figure 3. Bosentas 62.5 has released 100% of drugwithin 2 hours. Cumulative percent of bosentan released vs. time data from pellets are represented in the drug release profiles are shown in Figure 3.

The results indicated that slow and sustained release of bosentan from percentage weight gain of pellets in coating. During the first hour the % drug released values were found to be in the range of 13.21-19.80%.

The results indicated that increased coating weight decreased the drug release. This was observed in all the formulations. The formulations PC1, PC2 coated with 2.5%, 5% of weight gain from which 25% of the drug was released within 2 hours. Formulations PC3, PC4

coated with 7.5%, 10% of weight gain pellets released 25% of the drug in 2 hours. Formulations PC5, PC6 coated with 12.5%, 15% weight gain pellets released 25% of the drug in 2.5 hours.

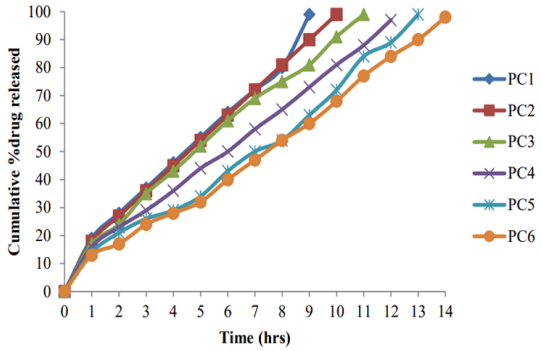

Figure 4: Bosentan release profile of PC1 to PC6 pellets (0-2 hrs 0.1N HCl; From 2 hours on wards pH 6.8 phosphate buffer).

Dissolution data indicated that the release of drug from the pan coated pellets was dependent on the weight gain of polymer coating.[14] It was found that as weight gain of polymer coating increased, release of drug from matrices decreased. It may be due to slower penetration of dissolution medium into hydrophobic matrices formed by eudragit RS100. Increased weight gain of polymer coating caused relatively more retardation in drug release due to increase in path length for diffusion of drug with increased thickness of the coat.

5. SURFACE CHARACTERISTICS

Scanning Electron Microscope (SEM) was used to study the morphology of coated pellets. Optimized formulation PC4 pellet samples were mounted on double sided tape on aluminium stubs and sputter coated with gold and micrographs were taken at appropriate magnification (scale factor 0.676 µm pixel-1) for detailed visualization of the surface using Leo VP-435 (Leo Electron Microscope, UK) to characterize roughness and the distribution of pores and holes appearing at the surface. The images of Nonpareil seed and surface, optimized pellets and surface are shown in Figures.

It was found that surface of pellets was smooth and free from cavities and deformities. This might be due to optimization of inlet air temperature, pan speed and spray rate, which otherwise influences the mixing pattern and leads to sticking, roughness and weight gain of the pellets. Hence, all the pellets were observed to be spherical in shape. SEM also proved that uniform coating was done over pellets surface.

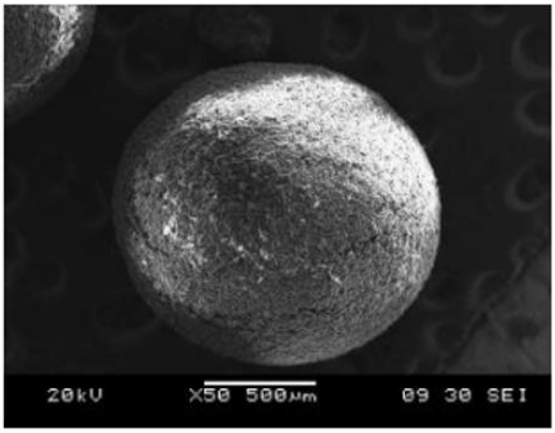

Figure 5: SEM of non pareil seed.

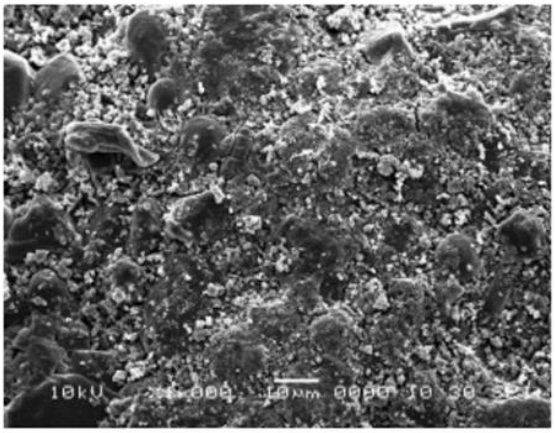

Figure 6: SEM showing nonpareil seed surface.

6. DRUG-EXCIPIENTS COMPATIBILITY STUDIES

Drug polymer compatibility studies were performed by FTIR in order to confirm that the entrapment of drug within the polymeric system involves only the physical process and no interaction persists with drug and polymer combination.

6.1 FTIR study

The spectra determined by using the Shimadzu FTIR 8300 spectrophotometer by KBr pellet method in the wavelength region of 4000 to 450 cm-1. The FTIR spectrum of pure drug bosentan, pure polymer Eudragit RS100 and optimized formulations are shown in Figures 8.10-8.12. The FTIR spectra of the pure bosentan showed band at 3064.25 cm-1 due to O-H stretching; 2962.86 cm-1 due to N-H stretching; 1292.32 cm-1 due to C-N stretching; 1453.42 cm-1 due to C-H bend; 1334.45 cm-1 due to N-O symmetric stretching, 1490 cm-1 due to N-O asymmetric stretching confirming the drug structure.

The FTIR spectrum of eudragit RS100 showed band at 3258.32 cm-1 due to – NH; 2923 cm-1 due to C-H; 986.58 cm-1 due to C-O stretching confirming the polymer structure. The FTIR spectrum of optimized formulation (PC4) showed all the characteristic bands of bosentan with minor shifts indicating the undisturbed drug in the formulation. This spectrum showed –OH stretch at 3061.14 cm-1, N-H stretch at 2960.32 cm-1, C-

N stretch at 1170 cm-1, C- H stretch at 1383.8 cm-1, N-O symmetricstretching at 1341.24 cm-1, N-O asymmetric stretching at 1504.14 cm-1 which confirms the undisturbed drug in the formulation.

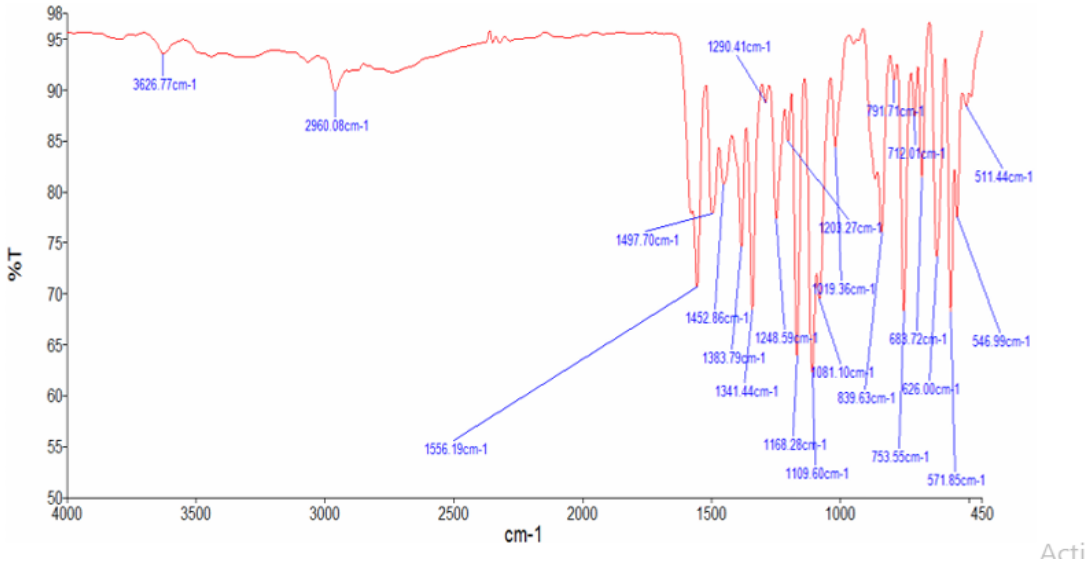

Figure 7: FTIR spectrum of bosentan.

CONCLUSION

Bosentan is a drug of choice for the treatment of pulmonary arterial hypertension. The absolute bioavailability of the bosentan is 50% and biological half life is 5 hours. Only immediate release dosage forms are available and there are no commercial controlled or sustained dosage forms for bosentan. Earlier reports indicated suitability of the drug for extending the release by using polymers like HPMC K100, HPMC 50 cps, karaya gum, xanthan gum, chitosan, carbopol 984, gelucire 43/01, compritol 888, poloxamer 407, poloxamer 188, polyethylene oxide in the form of matrix tablets, gastric floating beads, mini tablets, osmotic controlled release tablets. There are no reports on preparation of bosentan pellets by drug layering technology. Hence, in the present investigation it is proposed to formulate bosentan sustained release pellets by drug layering technology and subsequent coating with eudragit RS100 in pan coating process and ethyl cellulose in fluidized bed coating. With this objective, the present work was designed to prepare sustained release pellets of bosentan and achieve a desired in vitro release profile for a period of 12/24 hours by overcoming the variation in drug concentration in the plasma and to meet the therapeutic needs with improved patient compliance. Bosentan pellets were prepared and evaluated as described above. Based on the results the formulation CF12 (30% weight gain in coating) was optimized and the release profile was matching with predicted theoretical release based on f1 and f2 values.

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