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# DESIGN AND DEVELOPMENT OF SUSTAINED RELEASE PELLETS OF BOSENTAN BY PAN COATING PROCESS

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## ABSTRACT

The goal of the present study is to evaluate the influence of the formulation and operating conditions on pellet preparation by the pan technique. For this bosentan was selected as the model drug. Pellets were prepared by layering of powdered drug on sugar-based cores. Inert cores were intermittently treated with micronized drug powder and binding solution. This treatment led to the formation of multiple layers of drug particles around an inert core resulting in the production of pellets that can further be coated by different polymers to obtain modified release formulations. Scanning electron microscopy was employed to image the surface morphology of the prepared pellets. Drug loading efficiency, % yield, size and shape uniformity of pellets were increased along with increasing the initial core weight. Drug content and dissolution study were performed by following HPLC and UV–Visible method. The formulations were further characterized to identify any possible interactions by FTIR spectroscopy and differential scanning calorimetry. The surface morphology of the pellets was studied by scanning electron microscopy.

**KEYWORDS:** Bosentan, pellets, pan coating, surface morphology, binding solution.

## INTRODUCTION

Coating pans have been used in pharmaceutical coating operations since the early 19th century when they were used extensively for sugar coating.[1] The first pelletization process for developing a sustained release dosage form in the coating pan can be traced to the 1956 patent by Blythe. This process involved layering a drug powder onto nonpareils using syrup as the adhesive solution. There have been 30 years of research and development experience

in the powder layering technology since that patent and a variety of products have been successfully developed and introduced into the market.[2] With time, the manufacture of pellets in conventional coating pans has developed from the art of earlier years into a much more sophisticated and controlled process. The basic components of conventional coating pan system are the rotating pan, air supply system, spray system, powder addition system, and air–exhaust system. In the powder layering technology, pellets are usually prepared by loading the micronized powders on the solid cores. Generally, this pelletization method involves the using of inert substrates, such as sugar spheres and their enlargement by intermittently spraying a binder solution[3] and applying the active substance powder in a rotating coating pan or in a fluidized bed.[4] Once the drug beads are prepared, they may be further coated with a protective coating to allow a sustained or prolonged release of the drug.[5] Using a multiple-unit dosage form, pellets offer several advantages: Pellets disperse freely in the gastrointestinal tract and thus maximize drug absorption, reduce peak plasma fluctuations, and minimize side effects; high local concentrations of drug are avoided; there is flexibility in the development of oral dosage forms as pellets, so different drug substances (e.g. incompatible drugs) can be formulated and blended into a single dosage form; and immediate- and controlled-release pellets can be mixed to achieve the desired release pattern.[6-10]

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.[11]

The aim of the present research was mainly concentrated on the formualtion and evaluation of sustained release pellets of bosentan with different concentrations of eudragit RS100 by employing pan coating technique.

## MATERIALS AND METHODS

### Materials

Bosentan was obtained as gift sample from Dr. Reddy's laboratories, Hyderabad, India. Eudragit RS 100 was obtained as gift samples from Dow Chemical's Asia pvt. Ltd., Mumbai. Isopropyl alcohol, dibutyl phthalate were obtained from Loba chemi Pvt. Ltd., Mumbai.

**Methods**

Nonpareil seeds were then transferred to the conventional coating pan having 20 cm diameter, baffled and pear shaped which was constructed with stainless steel. The varying concentration of coating solutions were formed by using eudragit RL100 in isopropyl alcohol with nonstop stirring for about 1hr and lastly dibutyl phthalate was incorporated to it. The speed of pan was set at 30 rpm. The coating solution was sprayed by using spray gun manually on drug loaded pellets. At the temperature of 40-45$^0$C the inlet air was locked and with intermittent spraying and drying the coating was done manually. Hot air oven was used for 3 hr at 40$^o$C for drying of coated pellets. While coating operation all the necessary parameters must be observed wisely to obtained the better coating. Negligence from any one of coating related parameter may have direct impact on the quality of the product.

***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 formulated pellets were evaluated for various parameters. The results of the bulk density study concluded that the bulk density of all pellets was less than 1gm/ml. The value of angle of repose for all the batches of pellets was present from 9.440 to 11.210. As pellets of all the batches depicted angle of repose less than 20 hence excellent characteristic of flow was noted. After observing the table for friability study it was clearly seen that the friability for all the batches of pellets was less than 1%. Means the pellets were good. It was found after the study of SEM of pellets that surfaces of pellets was smooth and free from cavities and deformities. All the pellets were observed to be spherical in shapes. SEM also proved that uniform coating was done over pellets surfaces. DSC is an advanced technique by which the heat flows to or from a reference, which is monitored as a function of temperature or time, while the samples are subjected to a controlled temperature program. Thermal properties of pure drug were evaluated by Differential scanning caloriemetry using a diamond (DSC) (Mettler star 8.10). Accurately weighed 5-6 mg samples were hermetically sealed in aluminium pans and heated at a rate 50 $^{O}$C/min from 50$^{0}$C to 250 $^{0}$C temperature range under nitrogen flow of 25 ml/min. Results of DSC thermogram of pure Bosantan shows sharp endothermic peak at 107.49 $^{O}$C confirms the crystalline nature of the Bosentan. The infrared spectra of bosentan pure drug alone and mixture of drug with excipients were recorded between 450 – 4000 cm$^{-1}$ on Perkin Elmer FTIR. The FTIR spectra of the pure bosantan show spectrum peak points at 752, 1020, 1083, 1112,1203, 1252, 1292, 1453, 1579, 2962, 3064 and 3629 ± 1 cm$^{-1}$. The same peaks were appeared in the blend of drug with excipients. This indicated that there was no interaction between adrug and excipients.

The dissolution revealed that batch AF1 released the highest quantity of medicament and batch AF15 removed the least amount of medicament in 18 hr. It was happened due to the fact that batch AF1 contains less Eudragit RL 100 and batch AF15contains more quantity of eudragit RL 100. The study was performed in triplicate style and batch AF9 released 91.33 % of medicament in 18 hr of study. As the released pattern of batch AF9 was best suited to the present designed research work and hence it was optimized. All the formulations were found to have following typical Zero order kinetics which was clearly indicated by their relatively higher $r^2$ values compared to that of First order regression co efficient values. All the

formulations were found to be accepting Higuchian diffusion as release model, indicated by their relatively higher $r^2$values compared to that of Erosion model regression coefficient values. The dissolution data of all formulations were fitted to the Power law (Korsemeyer Pappas model) and the entire exponent 'n' values were found to be between 0.5-1, indicating that all the formulations were following Non-Fickian mode of drug release.

**Table 1: Formulation of drug loaded pellets.**

| S. No | Ingredients (gm) | AF1 | AF2 | AF3 | AF4 | AF5 | AF6 | AF7 | AF8 | AF9 | AF10 | AF11 | AF12 | AF13 | AF14 | AF15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Bosentan | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 |
| 2 | Eudragit RS 100 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 |
| 3 | Nonpareil seeds | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| 4 | Isopropyl alcohol(ml) | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |
| **Composition of coating solution** | | | | | | | | | | | | | | | | |
| 1 | Eudragit RS100 | 1.5 | 2 | 2.5 | 3 | 3.5 | 4 | 4.5 | 5 | 5.5 | 6 | 6.5 | 7 | 7.5 | 8 | 8.5 |
| 2 | Isopropyl alcohol | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |
| 3 | Dibutyl phthalate | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

**Table 2: Physical properties data of pellets.**

| Batch | Bulk density (gm/ml) | Tapped density (gm/ml) | Angle of repose ($^0$) | % friability | % drug content |
|---|---|---|---|---|---|
| AF1 | 0.78±0.015 | 0.80±0.025 | 10.18 | 0.04 | 19.07±0.25 |
| AF2 | 0.71±0.009 | 0.86±0.091 | 10.38 | 0.05 | 19.10±0.34 |
| AF3 | 0.79±0.004 | 0.86±0.004 | 11.22 | 0.03 | 19.16±0.11 |
| AF4 | 0.81±0.023 | 0.81±0.011 | 9.44 | 0.03 | 20.57±0.24 |
| AF5 | 0.79±0.004 | 0.88±0.012 | 9.54 | 0.04 | 21.34±0.14 |
| AF6 | 0.73±0.022 | 0.84±0.022 | 10.18 | 0.05 | 19.89±0.14 |
| AF7 | 0.82±0.008 | 0.82±0.008 | 10.32 | 0.04 | 19.36±0.63 |
| AF8 | 0.76±0.025 | 0.87±0.025 | 11.48 | 0.05 | 19.86±0.52 |
| AF9 | 0.76±0.025 | 0.82±0.011 | 9.88 | 0.06 | 19.78±0.21 |
| AF10 | 0.80±0.003 | 0.80±0.009 | 9.52 | 0.03 | 20.13±0.13 |
| AF11 | 0.72±0.007 | 0.81±0.008 | 10.65 | 0.06 | 19.07±0.21 |
| AF12 | 0.72±0.007 | 0.88±0.007 | 11.29 | 0.05 | 20.21±0.32 |
| AF13 | 0.75±0.004 | 0.88±0.08 | 9.71 | 0.04 | 19.13±0.57 |
| AF13 | 0.74±0.012 | 0.84±0.011 | 11.38 | 0.03 | 20.21±0.57 |
| AF14 | 0.77±0.018 | 0.86±0.012 | 11.29 | 0.05 | 19.97±0.13 |
| AF15 | 0.74±0.005 | 0.83±0.004 | 9.71 | 0.06 | 19.74±0.24 |

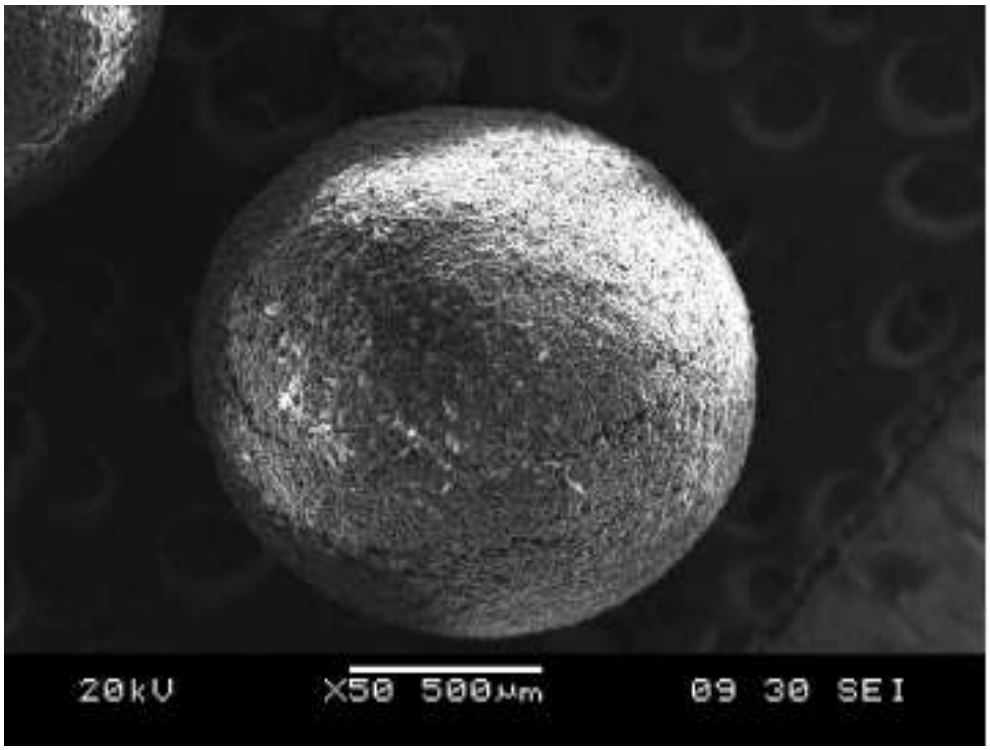



**Figure 1: SEM of bosentan pellet.**

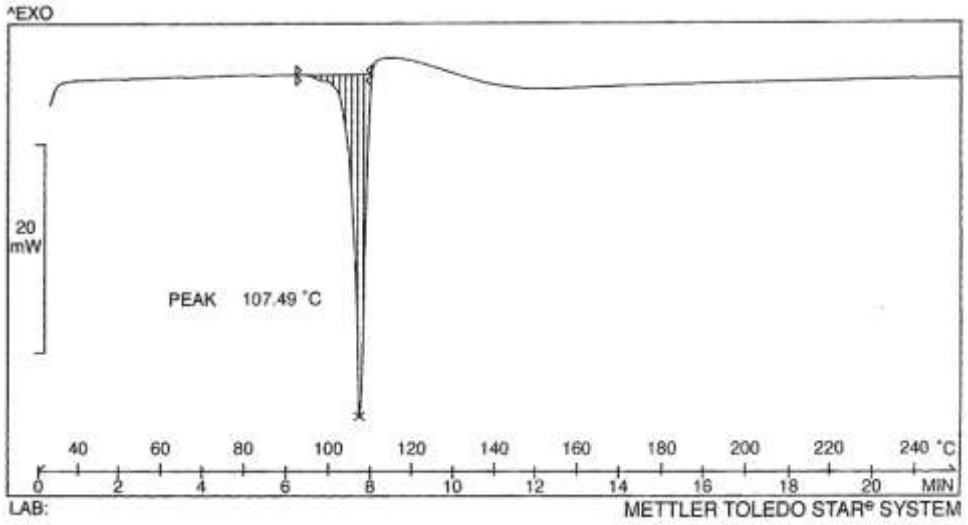



**Figure 2: DSC thermogram of bosentan.**

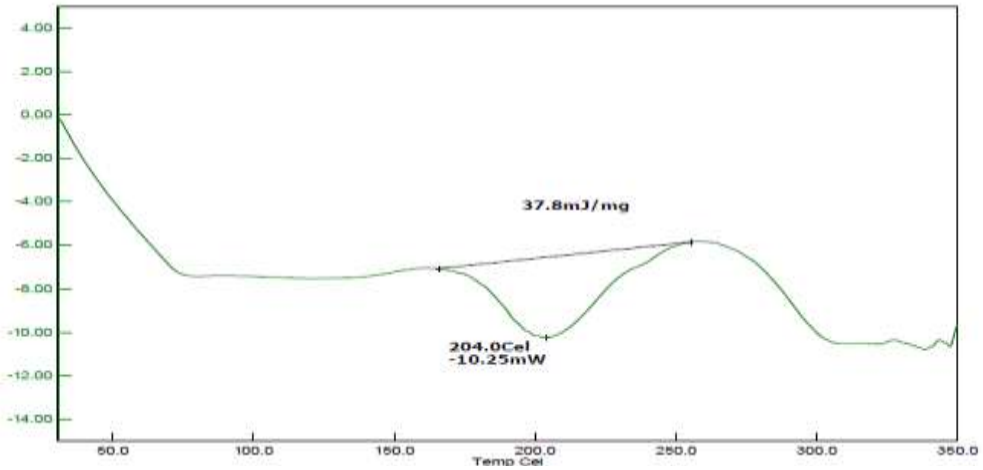



**Figure 3: DSC thermogram of Eudragit RL100.**

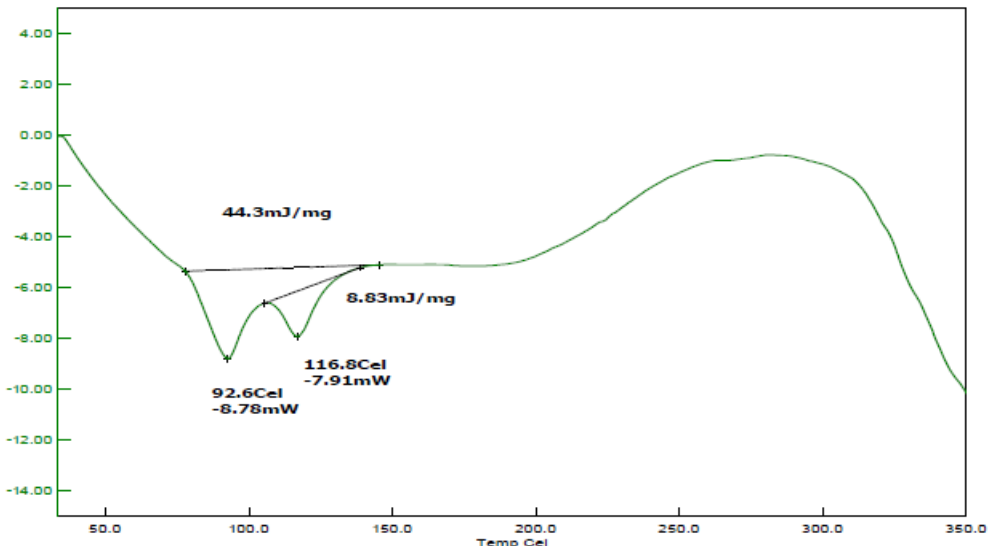
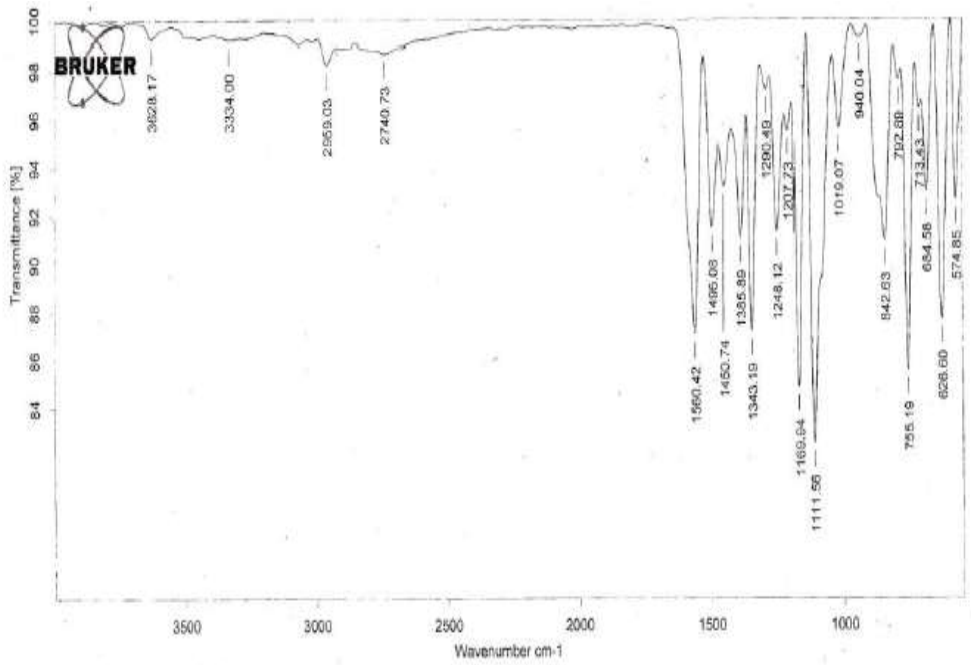
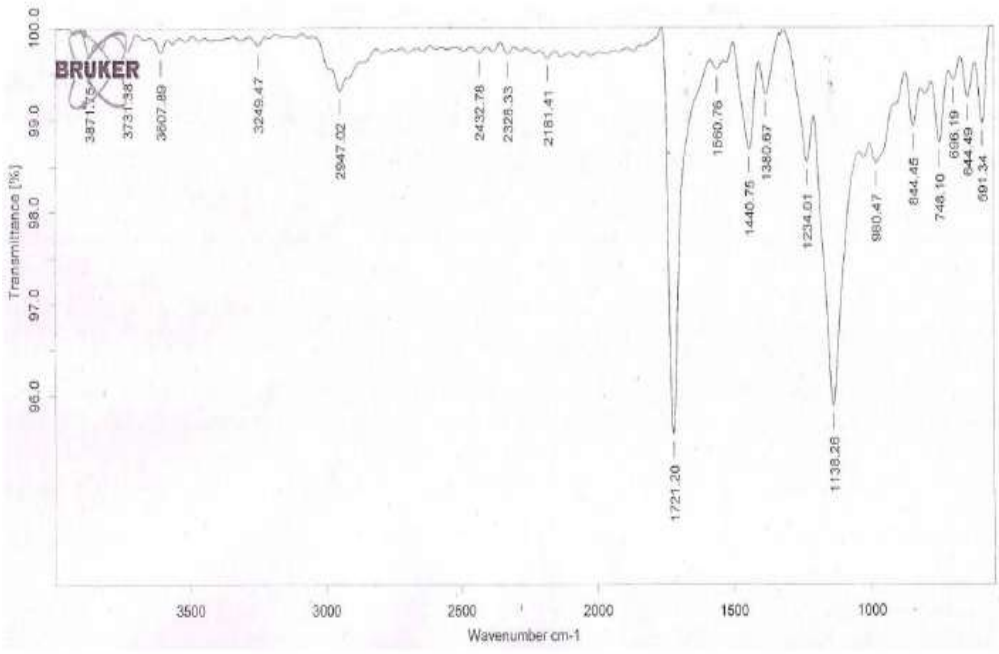



**Figure 4: DSC thermogram of Drug+Eudragit RL100.**

**a)**


BRUKER
Transmittance [%]
100
98
96
94
92
90
88
86
84
3628.17
3334.00
2959.03
2740.73
1560.42
1496.08
1450.74
1385.89
1343.19
1290.49
1248.12
1207.73
1169.64
1111.56
1019.07
940.04
842.63
792.88
755.19
713.43
684.56
626.60
574.85
3500
3000
2500
2000
1500
1000
Wavenumber cm-1

**b)**


BRUKER
Transmittance [%]
100.0
99.0
98.0
97.0
96.0
3731.38
3607.89
3249.47
2947.02
2432.78
2325.33
2181.41
1721.20
1660.76
1440.75
1380.67
1234.01
1138.26
980.47
844.45
746.10
696.19
644.49
591.34
3500
3000
2500
2000
1500
1000
Wavenumber cm-1

**c)**

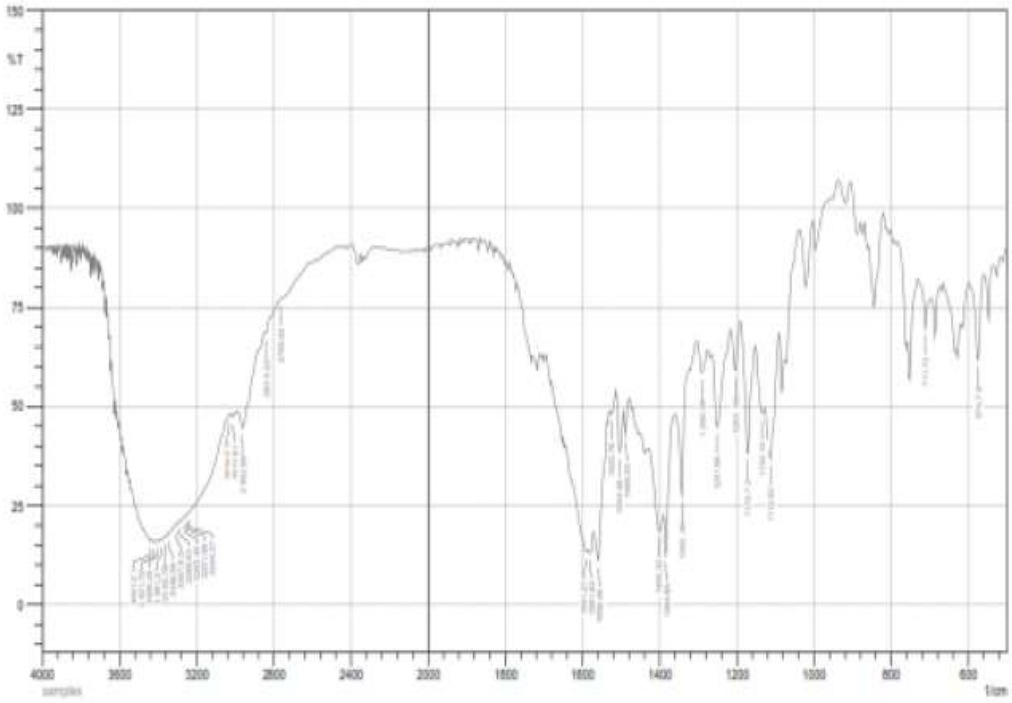


**Figure 5: FT-IR spectrum of a)bosentan b) Eudragit RL100 c)physical mixture bosentan+ Eudragit RL100.**

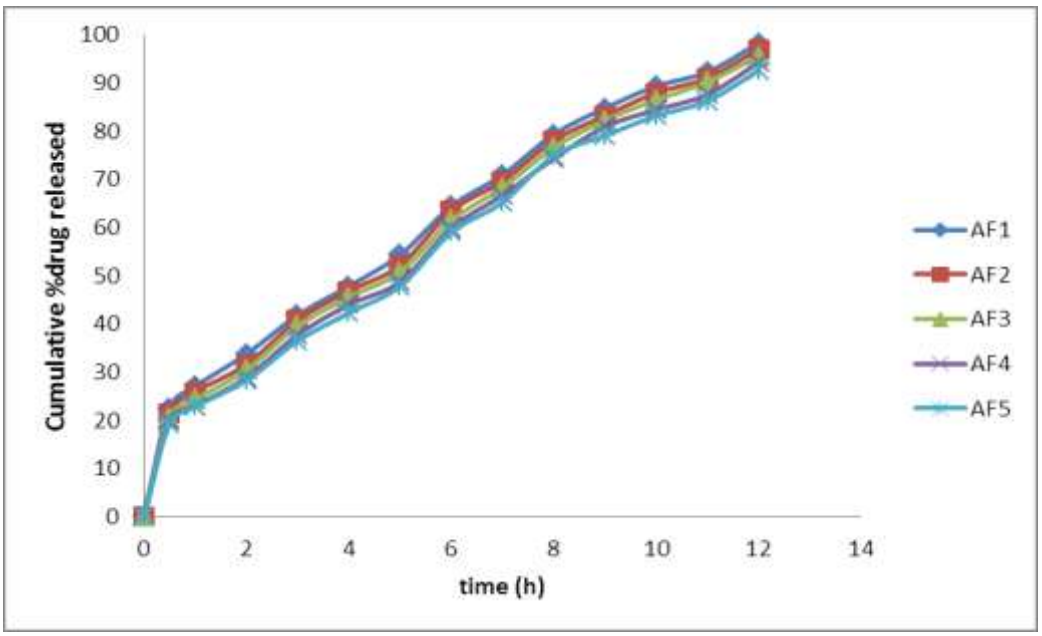



**Figure 6: Drug release profile of AF1 TO AF5 formulations.**

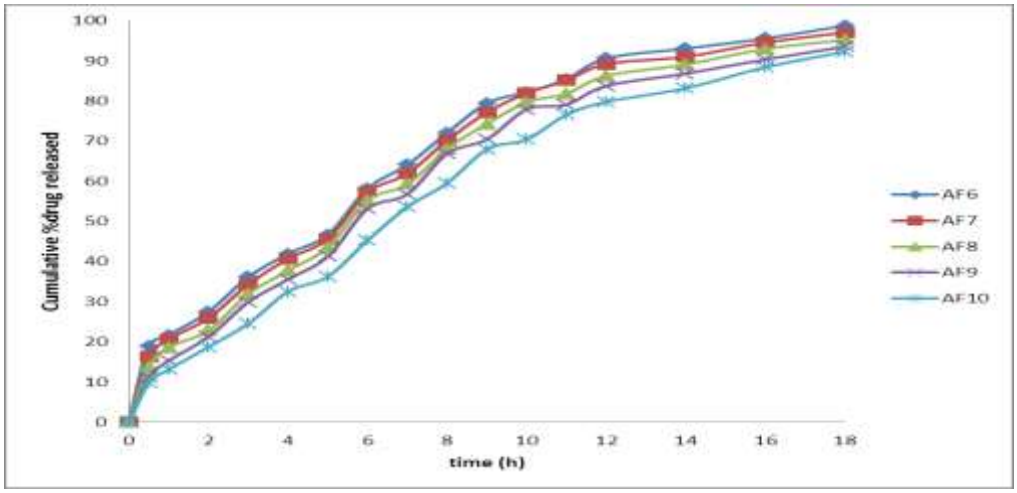



**Figure 7: Drug release profile of AF6 TO AF10 formulations.**

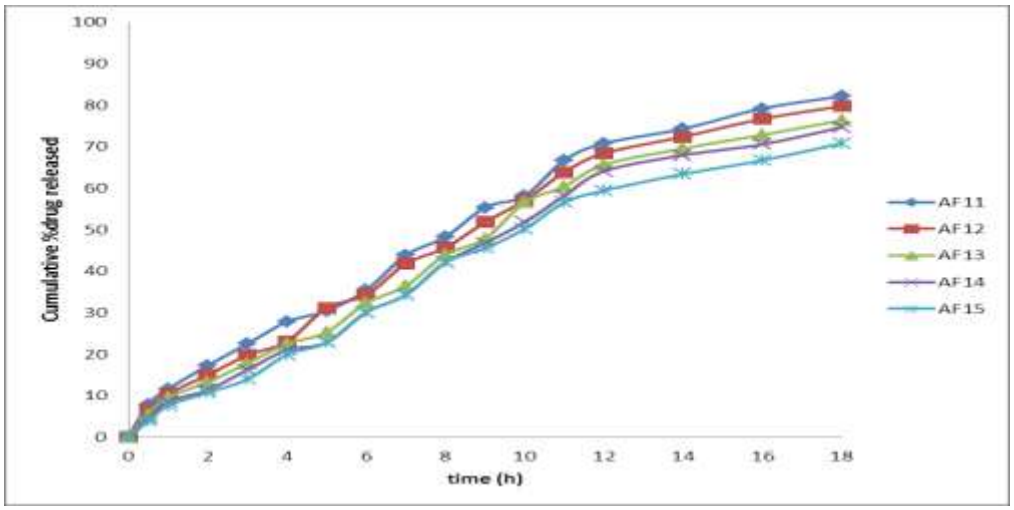



**Figure 8: Drug release profile of AF11 TO AF15 formulations.**

**Table 3: Kinetic drug release data of bosentan from AF1 TO AF15 formulations.**

| Formulation code | Zero order | First order | Higuchi | Korsemeyer pepas | 'n' value |
|---|---|---|---|---|---|
| AF1 | 0.9913 | 0.8588 | 0.9799 | 0.9693 | 0.49 |
| AF2 | 0.9906 | 0.8799 | 0.9782 | 0.9671 | 0.51 |
| AF3 | 0.9916 | 0.9237 | 0.9775 | | 0.52 |
| AF4 | 0.9915 | 0.9317 | 0.9746 | 0.9628 | 0.53 |
| AF5 | 0.9906 | 0.9416 | 0.9726 | 0.9619 | 0.53 |
| AF6 | 0.9900 | 0.9593 | 0.9726 | 0.9608 | 0.54 |
| AF7 | 0.9916 | 0.9636 | 0.9749 | 0.9719 | 0.57 |
| AF8 | 0.9896 | 0.9730 | 0.9730 | 0.9739 | 0.61 |
| AF9 | 0.9892 | 0.9782 | 0.9768 | 0.9845 | 0.67 |
| AF10 | 0.9941 | 0.9736 | 0.9668 | 0.9776 | 0.7 |
| AF11 | 0.9961 | 0.9647 | 0.9581 | 0.9855 | 0.69 |
| AF12 | 0.9976 | 0.9695 | 0.9596 | 0.9846 | 0.74 |
| AF13 | 0.9939 | 0.9624 | 0.9432 | 0.9816 | 0.77 |
| AF14 | 0.9926 | 0.9601 | 0.9378 | 0.9808 | 0.81 |
| AF15 | 0.9951 | 0.9770 | 0.9052 | 0.9498 | 0.85 |

## CONCLUSION

The multiunit dosage form, pellets that were formulated by drug layering technique showed optimized sustained release of the drug bosentan for extending the drug release for a prolonged period of time. Drug loaded pellets were coated with eudragit RS 100 at different concentrations.

The pellets gave more controlled fashion of drug release than sustained matrix formulations.

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