**Preparation and Evaluation of Sustained Release Matrix Tablets of Bosentan by Using Wet Granulation Technique**

Y. Ganesh Kumar 1 *, J. Sreekanth2, D. Satyavati3

1Research Scholar, Faculty of Pharmaceutical Sciences, JNTU, Kukatpally, Hyderabad, Telangana, India.

2Sr. General Manager, R&D Center, MSN Laboratories Pvt. Ltd, Hyderabad, Telangana, India.

3Brilliant Group of Institutions (Integrated Campus), Abidnagar, Hayathnagar, R.R Dist, Telangana, India.

*Corresponding author’s E-mail: ganesh.yed@gmail.com

**ABSTRACT**

The objective of the present study was to develop Bosentan monohydrate matrix tablets, sustained release dosage form, for the treatment of Pulmonary Arterial Hypertension Disease. Drug Excipient Compatibility study was performed through FTIR and DSC revealed that there no interaction between drug and polymers. Matrix tablets were prepared by wet granulation method using different concentration of Compritol 888 ATO, Poloxamer-407, and Poloxamer-188. Prepared formulations were subjected to Pre-compression parameters like angle of repose, bulk and tapped density, Hausser’s ratio and car’s index and post-compression parameters like hardness, friability, thickness, % drug content, and weight variation. All the formulations resulted in acceptable Pharmacopoeia limits. Tablets were subjected to In-Vitro drug release in 0.1 N HCl (pH 1.2) for first 2 hours followed by phosphate buffer (pH 6.8) for remaining 10 hours. The optimized formulation (F6) on the basis of acceptable tablet properties and In Vitro drug release. The resulting formulation produced robust tablets with optimum hardness, consistent weight uniformity and friability. A decrease in release kinetics of the drug was observed on increasing polymer ratio. Among all these formulations F-6 is optimized Based on Cumulative % Drug Release was found to be 97.5 ± 0.91 % in 12 hrs. In this formulation containing 62.5 mg of Bosentan Pure drug, 93.75mg of Poloxamer, PVP K-30, 6mg of Talc, 6mg of MgStearate, and 131.75mg of MCC. As the result of this study it may conclude that the formulation meet the needed theoretical drug release profile and has the sustain action i.e., retarding the drug release so the release is for a long time and thus more Bioavailability.

**Keywords:** Bosentan, Poloxamer, Compritol 888 ATO, Wet granulation method, Sustained release Matrix Tablets

**INTRODUCTION**

Bosentan is a endothelin receptor antagonist used in the treatment of Pulmonary artery hypertension (PAH). It is readily absorbed from the gastrointestinal tract with oral bioavailability of about 50% and a plasma elimination half-life is 5 hours.

Oral dosage forms has long been the most popular and convenient route of drug delivery. Various types of modified release formulations have been developed to improve the patient compliance and also clinical efficacy of the drug. The sustained release oral dosage forms have been demonstrated to improve therapeutic efficacy by maintaining steady state drug plasma concentration.

Sustained release dosage forms are designed to complement the pharmaceutical activity of the medicament in order to achieve better selectivity and longer duration of action.

Sustained release preparations are helpful to reduce the dosage frequency and side effects of drugs and improve patient’s convenience.

Sustained release matrix tablet is relatively easy to fabricate by incorporating drug molecules in slowly disintegrating or inert porous materials.

The most commonly used method of modulating the drug release is to include it in a matrix system.

**MATERIALS AND METHODS**

**Materials**

Bosentan was provided by MSN Laboratories Pvt. Ltd, Hyderabad, Compritol888 ATO, Poloxamer-407 and Poloxamer-188 was procured from Yarrow chem. Products, Mumbai, PVP-K 30, Talc, Magnesium stearate, and MCC was bought from Signet Chem., Mumbai.

**Preformulation Studies**

**Standardization of Bosentan by UV-Visible Spectrophotometry in 0.1 N HCl Solutions**

**Preparation of stock solution**

Stock solution 100µg/ml of Bosentan was prepared in 0.1N HCl solution. This solution was approximately diluted with 0.1N HCl to obtain a concentration of 10µg/ml. The resultant solution was scanned in range of 200-400nm using UV double beam spectrophotometer (Lab India UV-3000+).

**Standard calibration of Bosentan in 0.1N HCl**

100mg of Bosentan was accurately weighed and dissolved in100ml of 0.1N HCl to obtain a concentration of 1000µg/ml. From the above 10ml was withdrawn and diluted to 100ml to obtain a concentration of 100µg/ml. From this stock solution aliquots of 0.5ml, 1ml, 1.5ml, 2ml and 2.5ml were diluted in 10ml volumetric flask with phosphate buffer to give concentrations in range of...
10µg/ml to 70µg/ml respectively, absorbance was measured at 242 nm.

**Standardization of Bosentan by UV-Visible Spectrophotometry in pH 6.8 Solutions**

**Preparation of stock solution**

Stock solution 100µg/ml of Bosentan was prepared in phosphate buffer of pH 6.8. This solution was approximately diluted with phosphate buffer of pH 6.8 to obtain a concentration of 10µg/ml. The resultant solution was scanned in range of 200-400nm using UV double beam spectrophotometer (Lab India UV-3000+).

**Standard calibration of Bosentan in phosphate buffer of pH 6.8**

100mg of Bosentan was accurately weighed and dissolved in 100ml of pH 6.8 phosphate buffer to obtain a concentration of 1000µg/ml. From the above 10ml was withdrawn and diluted to 100ml to obtain a concentration of 100µg/ml. From this stock solution aliquots of 0.5ml, 1ml, 1.5ml, 2ml and 2.5ml were diluted in 10ml volumetric flask with phosphate buffer to give concentrations in range of 5µg/ml to 20µg/ml respectively, absorbance was measured at 243 nm.

**Drug-Excipient Compatibility by FTIR studies**

In the preparation of Sustained Release tablet, drug and polymer may interact as they are in close contact with each other, which could lead to instability of drug. Preformulation studies regarding drug-polymer interactions are therefore very critical in selecting appropriate polymers.

FT-IR spectroscopy (Agilent) was employed to ascertain the compatibility between bosentan and selected polymers. The individual drug and drug with excipients were scanned separately.

**Procedure**

Potassium bromide was mixed with drug and polymer in the ratio of 100:1 and pellet was prepared using KBr pellet press and spectrum was taken using FTIR (Agilent). FT-IR spectrum of bosentan was compared with spectrum of bosentan and polymer. Disappearance of bosentan peaks or shifting of peak in any of the spectra was studied.

**Evaluation of Granules**

**Angle of repose**

The angle of repose of blends was determined by the funnel method. The accurately weighed blend was taken in funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the blend. The blend was allowed to flow from the funnel on the surface. The diameter and height of the heap formed from the blend was measured. The angle of repose was calculated using following formula:

\[
\tan \theta = \frac{h}{r}
\]

Where, “h” is height of the heap and “r” is the radius of the heap of granules.

**Carr’s compressibility index**

The Carr’s compressibility Index was calculated from Bulk density and tapped density of the blend. A quantity of 2g of blend from each formulation, filled into a 10ml of measuring cylinder. Initial bulk volume was measured, and cylinder was allowed to tap from the height of 2.5cm. The tapped frequency was 25±2 per min to measure the tapped volume of the blend. The bulk density and tapped density were calculated by using the bulk volume and tapped volume.

Carr’s compressibility index was calculated by using following formula.

\[
\text{Carr’s compressibility index} (\%) = \frac{\left(\text{Tapped density} - \text{Bulk density}\right) \times 100}{\text{Tapped density}}
\]

**Bulk Density (BD)**

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced in to a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume. The bulk densities (BD) of powder blends were determined using the following formula:

\[
\text{Bulk density} = \frac{\text{Total weight of powder}}{\text{Total volume of powder}}
\]

**Tapped bulk density (TBD)**

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The tapped bulk densities (TBD) of powder blends were determined using the following formula:

\[
\text{TBD} = \frac{\text{Total weight of powder}}{\text{Total volume of tapped powder}}
\]

**Preparation of Matrix Tablets**

Bosentan tablets with different concentrations of polymer were prepared by the wet granulation technique.

**Wet Granulation Method**

All the powders were passed through 80 mesh. Required quantities of all ingredients were mixed thoroughly and a sufficient volume of granulating agent was added slowly. After enough cohesiveness was obtained, the mass was sieved through 22/44 mesh. The granules were dried at 40 C for 12hrs. Once, dry the granules retained on 44 mesh were mixed with 10% of fine granules that passed through 44 mesh. Talc and magnesium stearate were added as glidant and lubricant. In all formulations, the amount of the active ingredient is equivalent to 62.5 mg of Bosentan (Table 1).
Table 1: Formulations Containing Compritol 888 ATO, Poloxamer-407, 188 (Wet granulation)

<table>
<thead>
<tr>
<th>S. No</th>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
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<tr>
<td>1</td>
<td>Bosentan</td>
<td>62.5</td>
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<td>62.5</td>
<td>62.5</td>
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<td>2</td>
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<td>31.25</td>
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<td>----</td>
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<td>3</td>
<td>Poloxamer-407</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>31.25</td>
<td>62.5</td>
<td>93.75</td>
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<td>----</td>
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<tr>
<td>4</td>
<td>Poloxamer-188</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>31.25</td>
<td>62.5</td>
<td>93.75</td>
</tr>
<tr>
<td>5</td>
<td>PVP K-30</td>
<td>QS</td>
<td>QS</td>
<td>QS</td>
<td>QS</td>
<td>QS</td>
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<tr>
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<td>Mg. Stearate</td>
<td>6</td>
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<td>6</td>
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<tr>
<td>8</td>
<td>MCC</td>
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<td>163</td>
<td>131.75</td>
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<td>300</td>
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<td>300</td>
</tr>
</tbody>
</table>

Evaluation of Tablets

**Hardness test**

Hardness indicates the ability of a tablet to withstand mechanical strength while handling. The hardness of the tablets were determined using Monsanto Hardness tester. It is expressed in Kg/cm².

Three tablets were randomly picked from each formulation and the mean and standard Deviation values were calculated.

**Friability test**

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined by using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (Wt.initial) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (Wt.final). The percentage friability was then calculated by,

\[
\% \text{F} = \left( \frac{\text{loss in weight}^2}{\text{initial weight}} \right) \times 100
\]

% Friability of tablets less than 1% are considered acceptable.

**Weight variation test**

The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. To study weight variation, 20 tablets of each formulation were weighed using an electronic balance Aqua and the test was performed according to the official method.

**Drug Content**

Drug content of the tablets was determined by UV Spectrophotometrically.

**Uniformity of thickness**

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter was measured using vernier caliper.

**In vitro release studies**

Release of the prepared tablets was determined up to 12 hrs using USP type II paddle type dissolution rate test apparatus (Lab India). 0.1 N HCl (900 ml) was used as dissolution medium for first 2 hrs and phosphate buffer pH 6.8 for the rest of the period as dissolution medium. The paddle was adjusted at 50 rpm and the temperature of 37±0.5°C was maintained throughout the experiment. Samples were withdrawn at known time intervals and were replaced with same volume of fresh dissolution media after each withdrawal. The samples were analysed for drug contents by measuring absorbance by using UV spectrophotometer.

**Dependent-model method (Data analysis)**

In order to describe the Bosentan release kinetics from individual tablet formulations, the corresponding dissolution data were fitted in various kinetic dissolution models: zero order, first order, Higuchi, Korsmeyer Peppas. When these models are used and analyzed in the preparation, the rate constant obtained from these models is an apparent rate constant. The release of drugs from the matrix tablets can be analysed by release kinetic theories.

To study the kinetics of drug release from matrix system, the release data were fitted into Zero order as cumulative amount of drug release vs. time (Eqn.3), first order as log cumulative percentage of drug remaining vs. time (Eqn.4), Higuchi model as cumulative percent drug release vs. square root of time (Eqn.5). To describe the release behavior from the polymeric systems, data were fitted according to well known exponential Korsmeyer – Peppas equation as log cumulative percent drug release vs log of time equation (Eqn.6).
Zero order kinetics

\[ Qt = K_0 t \quad \text{Eqn. (3)} \]

Where, \( Q \) = Amount of drug release in time \( t \)
\( K_0 \) = Zero order rate constant expressed in unit of concentration/time
\( t \) = Release time

First order kinetics

\[ \log Q = \log Q_\infty - kt / 2.303 \quad \text{Eqn. (4)} \]

Where, \( Q_\infty \) is the initial concentration of drug
\( k \) = is the first order rate constant
\( t \) = release time

Higuchi kinetics

\[ Q = kt^{1/2} \quad \text{Eqn. (5)} \]

Where,
\( k \) = Release rate constant
\( t \) = release time, Hence the release rate is proportional to the reciprocal of the square root of time

Korsmeyer-Peppas

First 60% in vitro release data was fitted in equation of Korsmeyer to determine the release behavior from controlled release polymer matrix system. The equation is also called as power law,

\[ \frac{M_t}{M_\infty} = Kt^n \quad \text{Eqn. (6)} \]

Where,
\( M_t \) = amount of drug released at time \( t \)
\( M_\infty \) = amount of drug released after infinite time
\( Kt^n \) = fraction solute release
\( t \) = release time

For matrix tablets, values of \( n \) of near 0.5 indicates diffusion and erosion as overall release mechanism commonly called as anomalous release mechanism.7

RESULTS AND DISCUSSION

Preformulation characteristics

The drug Bosentan was standardized by UV method in 0.1N HCl and pH 6.8 Buffer separately. The \( \lambda_{max} \) were 242 nm and 243 nm in 0.1N HCl and pH 6.8 buffers respectively and the linearity range was 5-70 mcg/ml in both the media.

Compatibility Studies - FTIR

Drug polymer compatibility study was done by IR. The IR spectrum of Bosentan and physical mixture of drug and polymers were recorded using Agilent Technologies. The pellets were prepared in KBr press using physical mixture of drug, polymers and KBr. The spectra were recorded over the scanning range of 4000-400 cm.

![FTIR spectra of Bosentan pure Drug](image1)

![FTIR spectra of Bosentan pure Drug + Poloxamer-407](image2)

![FTIR spectra of Optimized Formulation (Bosentan + Poloxamer-407+PVP-K 0+Talc+Mg.Stearate+MCC)](image3)

![Differential Scanning Calorimetry analysis of Bosentan Pure Drug.](image4)

![Differential Scanning Calorimetry analysis of Optimized Formulation (Drug+ Poloxamer-407+ pvp k 30+ talc+ Mg.Stearate+ Mcc)](image5)
The compatibility and interactions between drugs and polymer were checked using differential scanning calorimetry (DSC). Any possible drug polymer interaction can be studied by thermal analysis. The DSC study was performed on pure drug (Bosentan) and Optimized Formulations (drug + Poloxamer-407 + pvp k 30 + talc + MgStearate + Mcc). The study was carried out using Hitachi 6300.

The 2 mg of sample were heated in a hermetically sealed aluminum pans in the temperature range of 30-220°C at heating rate of 10°C /min under nitrogen flow of
40ml/min. Finally hence their no interaction was found between drug and the polymers.

![Graph showing dissolution profiles of Formulations F1-F9](image)

**Figure 6:** Dissolution profiles of Formulations F1-F9

**Table 4:** Drug release kinetics studies of all formulations (F1-F9)

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>R² Value</th>
<th>Release exponent 'n'</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Zero order</td>
<td>First order</td>
</tr>
<tr>
<td>F1</td>
<td>0.9436</td>
<td>0.8553</td>
</tr>
<tr>
<td>F2</td>
<td>0.9333</td>
<td>0.9034</td>
</tr>
<tr>
<td>F3</td>
<td>0.9872</td>
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<td>F4</td>
<td>0.9755</td>
<td>0.9648</td>
</tr>
<tr>
<td>F5</td>
<td>0.9837</td>
<td>0.9238</td>
</tr>
<tr>
<td>F6</td>
<td>0.9803</td>
<td>0.7179</td>
</tr>
<tr>
<td>F7</td>
<td>0.9646</td>
<td>0.7866</td>
</tr>
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<td>F8</td>
<td>0.9722</td>
<td>0.8909</td>
</tr>
<tr>
<td>F9</td>
<td>0.9900</td>
<td>0.8690</td>
</tr>
</tbody>
</table>

**Physical characteristics of blends and tablets**

The blends of different formulations were evaluated for angle of repose, Carr’s compressibility index etc. The results of angle of repose and Carr’s compressibility Index (%) ranged from 16-28 and 14-16, respectively which showed that blends from all the formulations having good flow property. The hardness and percentage friability ranged from 3.5-5kg/cm² and 0.28-0.55% respectively.

**In vitro dissolution studies**

Bosentan monohydrate sustained release tablets were prepared by using different polymers. The release profiles of Bosentan sustained release tablets were plotted as Fig 7-9. Among all the formulations (F-1 to F-9) Contained Bosentan and Compritol 888 ATO, Poloxamer-407, and Poloxamer-188 Polymers in different ratios i.e., 1:0.5, 1:1 and 1:1.5.

It was found that drug release of among all the formulations, F-6 containing Poloxamer-407 in ratio of 1:1.5 could retard drug for relatively 12 hrs compared to all other formulations.

So Formulation (F-6) has showed maximum amount of drug released with drug release of 97.5±0.91 % in 12 hours, so it is chosen Optimized formulation.

**Phenomenon of Drug Release Kinetics**

The optimized formulation F6 was subjected to graphical representation to assess the kinetics of drug release. The release of drug was observed to follow the Zero order release kinetics. The initial burst effect was observed as per Zero order kinetics. Hence the drug release was mainly found to be concentration dependent. Hence we conclude that diffusion is the mechanism of drug released.

**CONCLUSION**

The purpose of the present study was to formulate and evaluate SR matrix tablets of Bosentan was prepared by wet granulation method by using different polymers of Compritol 888 ATO, Poloxamer grades.

IR spectra indicated the absence of probable chemical interaction between the drug and polymers used in three different proportions. Melting point of Bosentan was found to be 116.4° C. Characterization of granules prepared by selected manufacturing processes like bulk density, tapped density, Carr’s index, Hausner’s ratio, Angle of repose was done and Found to have good flow and compressibility. The tablets prepared were found to be within the limits with respect to hardness, weight variation, % friability, thickness and in vitro dissolution study. In-vitro dissolution studies of the formulation (F6) showed complete release of drug in 12 hrs.

The optimized formulation of F6 is the best in vitro release of 97.5±0.91 % in 12 hrs in simulated intestinal fluid. The release of drug followed matrix diffusion mechanism. Under the study of kinetic models, Four models have been studied namely Zero Order, First Order, Higuchi, Korsmeyer’s-Peppas model. It was found that the drug release followed Zero order kinetic having maximum R² value is 0.9803.

**REFERENCES**


