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Formulation Development of Solid Dispersions of Bosentan using Gelucire 50/13 and Poloxamer 188

Tapan Kumar Panda*, Debajyoti Das, Lalatendu Panigrahi

School of Pharmaceutical Sciences, SOA University, Bhubaneswar, Odisha, India.

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ABSTRACT

The objectives of the present research work are to improve the solubility and dissolution rate of bosentan. Solid dispersions of bosentan were prepared by fusion method by using two selected hydrophilic meltable carriers vis-à-vis gelucire 50/13 and poloxamer 188. Sylysia 350 was used as an adsorbent. Solid dispersions were evaluated for solubility, phase solubility, flowability, compressibility, Fourier transform infrared spectra (FT-IR), differential scanning calorimetry (DSC). Solubility studies showed 8 and 10 fold increase in solubility for gelucire 50/13 and poloxamer 188 based solid dispersions respectively. The Gibbs free energy $\Delta G_{tr}°$ values were all negative for gelucire 50/13 (0, 0.1, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8 and 10 % w/v) and poloxamer 188 (0, 0.1, 0.25, 0.5, 0.75 and 1 % w/v) indicating spontaneous nature of solubilisation. FT-IR and DSC spectra showed that drug and carriers are compatible with each other. Solid dispersions exhibiting highest solubility were compressed into immediate release tablets by using sodium starch glycolate as superdisintegrant. *In vitro* dissolution studies, exhibited more than 90 % drug dissolution in 1 h. Gelucire 50/13 and poloxamer 188 plays a significant role in enhancement of drug solubility and dissolution. The adsorbent, sylysia 350 may be used to impart good flow and compressibility to solid dispersions. Among the two carriers, poloxamer 188 exhibited better solubility and dissolution enhancement potential.

INTRODUCTION

According to biopharmaceutical classification system (BCS), drugs exhibiting high membrane permeability and low aqueous solubility are categorized under class II (Dahan *et al.*, 2009). The solubility or dissolution rate of drugs in this category is therefore a critical factor in determining the rate and extent of its absorption. Enhancement of the dissolution rate is vital for quick onset of therapeutic effect, as their dissolution rates are typically the rate-limiting step for bioavailability (Savjani *et al.*, 2012). Several approaches have been reported for enhancement of solubility of poorly water-soluble drugs, vis-a vis particle size reduction, surfactant systems, water soluble complexes, prodrug, lyophilization, solid state manipulation, solid dispersions etc (Sruti *et al.*, 2013). Among them solid dispersion is preferred because of ease of preparation and feasibility of scale up. Solid dispersion can be defined as distribution of active ingredients in molecular, amorphous, and/or crystalline forms surrounded by an inert carrier (Shamsuddin *et al.*, 2016). Formulation of poorly water-soluble drugs as solid dispersions leads to a marked improvement in their dissolution rates and is often accompanied by an increase in their relative bioavailability (Brough *et al.*, 2016). Recently, many researchers have reported significant improvement in solubility and dissolution rate for poorly soluble drugs by using meltable hydrophilic carriers like gelucire 50/13 (polyglycolized glyceride) and poloxamer 188 (Patel *et al.*, 2014). Gelucire is a varying mixture of mono, di and triglycerides with polyethylene glycol esters of fatty acids. They are inert, semisolid and waxy amphiphilic excipients. A low hydrophilic–lipophilic balance (HLB) value in gelucire decreases the dissolution rate whereas high HLB value enhances the dissolution rate. The low HLB compounds are composed of partial glycerides while those with HLB values above 10 are mixtures of partial saturated glycerides and polyethylene glycol (PEG) esters.

* *Corresponding Author*
Email:tapanpandapharmacy@gmail.com

Gelucire 50/13 is a semisolid excipient with an HLB value of 13 and melting point of 50^0C. Its hydrophilic property and low melting point makes it a good choice for use as carrier in preparation of solid dispersions by fusion method (Eloy *et al.*, 2012). Poloxamers are polyoxyethylene-polypropylene block copolymer nonionic surfactants that have been widely used as wetting and solubilising agents. Poloxamer consists of hydrophilic corona ethylene oxide and hydrophobic core (polypropylene oxide) blocks arranged in a triblock structure resulting in an amphiphilic copolymer. Poloxamer 188 exhibits low melting point (about 52-57^0C) with an HLB value of 29. Poloxamer 188 based solid dispersions have been considered as an effective method for improving drug dissolution rate and their saturation solubility in the gastrointestinal fluids (Homayoun *et al.*, 2014).

Although gelucire 50/13 and poloxamer 188 based solid dispersions significantly enhance the dissolution rate of poorly water soluble drugs, but they have some limitations such as poor flow and sticking to tablet punches (El-Badry, 2011). This may be a problem in development of tablet or capsule dosage forms. In order to overcome these problems, an inert material with good flow and compressibility may be used to adsorb the dispersion on its surface. Sylysia is an amorphous SiO_2 with high specific surface area and porosity, is a dry, white micronized porous powder having an average particle size of 3.9 mm, and is tasteless and odorless. It has a high specific surface area (300 m^2/g) and high adsorption capacity (310 mL/100 g), making it a good material for adsorption of a high proportion of drug (Ahuja and Pathak, 2009. It is used primarily as a tablet excipient to improve the ease of powder flow through the tableting process, which provides more accurate dosage. It can be also used for powderizing liquids, to increase the viscosity of liquids and gels, or to protect sensitive compounds from moisture.

Bosentan is a BCS class II drug, demonstrating approximate 50% absolute bioavailability (Weber *et al.*, 1996). Bosentan is a dual endothelin receptor antagonist indicated mainly in the management of pulmonary artery hypertension. It has also been investigated in heart failure and in hypertension (Weber *et al.*, 1999). In pulmonary hypertension, given by mouth in an initial dose of 62.5 mg twice daily, increased after 4 weeks to a maintenance dose of 125 mg twice daily. In patients with low body weight (below 40 kg) both the initial and maintenance dose are 62.5 mg daily (Gabbay *et al.*, 2007). Hence, the objectives of the present research work are to improve the solubility and dissolution rate of bosentan, to compare solubility enhancement potential between gelucire 50/13 and poloxamer 188 and to formulate the optimized solid dispersion into immediate release tablets.

MATERIALS and METHODS

Materials

Bosentan was received as gift sample from MSN Pharma, India. Gelucire 50/13 was received as gift sample from Gattefosse, India, Poloxamer 188 was procured from Sigma Aldrich, India. Sylysia 350 was obtained as a gift sample from Fuji Sylysia, Japan. Sodium starch glycolate was purchased from HiMedia, India. All other reagents and chemicals used were of analytical grade.

Methods

Pre-formulation Study

Phase solubility study

Phase solubility studies were performed as per method described by Higuchi *et al.*, 1965. An excess amount of powdered bosentan was placed in a screw-cap glass vial to which 20 mL of distilled water containing various concentrations (0, 0.1, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8 and 10 % w/v) of gelucire 50/13 (Table 1) and poloxamer 188 (0, 0.1, 0.25, 0.5, 0.75 and 1 % w/v) was added (Table 2).

The samples were shaken at 37 ± 0.5 °C for 72 h on a Remi mini rotary shaker-12R-DX. After 72 h of shaking, the samples were filtered through a 0.45 µm membrane filter (Auroco, Thailand). The filtrate was diluted suitably and analyzed in an UV-Vis spectrophotometer UV-1800 (Shimadzu, Japan).

Table 1: Effect of concentration of Gelucire 50/13 on Gibb's free energy.

Concentration of Gelucire 50/13 (% *w/v*)	Concentration of Bosentan (mg/mL)	ΔG_{tr}° (J/mol)*
0	0.121	0
0.1	0.627907	-1.646
0.25	0.732558	-1.801
0.5	0.837209	-1.934
0.75	0.993023	-2.105
1	1.14186	-2.245
2	1.35814	-2.418
4	1.888372	-2.748
6	2.25814	-2.92703
8	2.746512	-3.12286
10	3.260465	-3.29443

Table 2: Effect of concentration of Poloxamer 188 on Gibb's free energy.

Concentration of Poloxamer 188 (% *w/v*)	Concentration of Bosentan (mg/mL)	ΔG_{tr}° (J/mol)
0	0.125	0
0.1	0.512	-1.454
0.25	0.611	-1.613
0.5	0.723	-1.782
0.75	0.819	-1.901
1	0.876	-1.951

The value of the apparent stability constant, Ks for bosentan-gelucire 50/13 and bosentan-poloxamer 188 combinations was computed from the phase-solubility profiles, as described by;

$$Ks = {Slope}\Big/{Intercept\ (1 - Slope)} \qquad (1)$$

The Gibb's free energy of transfer (ΔG_{tr}^{0}) of bosentan from distilled water to solutions of carrier was calculated by using formula:

$$\Delta G_{tr}^{0} = -2.303RT\left\{log\frac{S_0}{S_s}\right\} \qquad (2)$$

Where S_0/S_s is the ratio of the molar solubility of bosentan in distilled water of gelucire 50/13 and poloxamer 188 to that in the same medium.

FT-IR spectroscopy study

Bosentan-carriers (1:1) interactions were assessed by FT-IR spectroscopy (IR-Affinity-1, Shimadzu, Japan). FT-IR spectra of pure drug bosentan and its 1:1 solid dispersions with gelucire 50/13 and poloxamer 188 were recorded on IR using KBr discs. The instrument was operated under dry air purge and the scans were collected at a scanning speed of 2 mm/sec with resolution of 4 cm^{-1} over the region 4000-400 cm^{-1}. The FT-IR spectra are shown in figure 1.

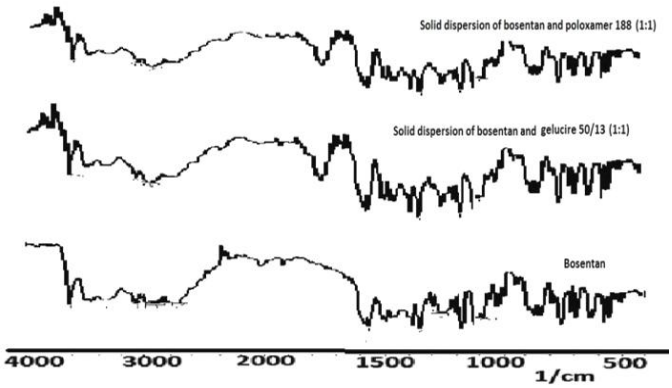

Fig. 1: Fourier transform infrared spectra of bosentan and its 1:1 solid dispersions with gelucire 50/13 and poloxamer 188.

Differential scanning calorimetry (DSC) study

The DSC measurements were performed on a DSC with thermal analyzer (DSC-60, Shimadzu, Japan). All the accurately weighed samples (about 2 mg) were placed in sealed aluminum pans before heating under nitrogen flow (20 mL/min) at a scanning rate of 10 °C/min from 25 to 175°C. An empty aluminum pan was used as reference. DSC measurements were performed for bosentan and its 1:1 solid dispersions with gelucire 50/13and poloxamer 188 to study drug carrier interaction. The results are shown in figure 2.

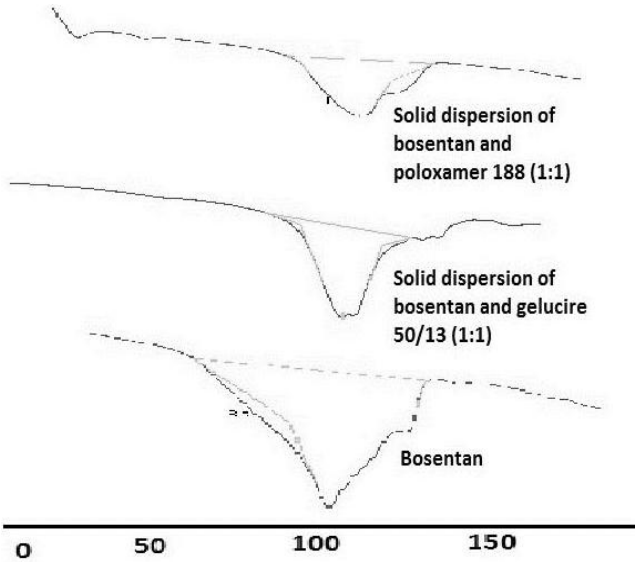

Fig. 2: Differential scanning calorimetry thermograms of bosentan and its 1:1 solid dispersions with gelucire 50/13 and poloxamer 188

Formulation of solid dispersion

Preparation of solid dispersions of Bosentan with Gelucire 50/13 and Poloxamer 188

Solid dispersions were prepared by fusion method. Bosentan was added to the melt of gelucire 50/13, maintaining a temperature of 60^0C to obtain a clear molten mixture. The molten mixture was then added drop-wise to sylysia 350 with continued mixing. The solid dispersions were allowed to cool to room temperature by air-cooling followed by sieving through mesh 30. The compositions of solid dispersions are shown in Table 2. Batch size of each formulation was 50 g. Poloxamer 188 based solid dispersions of bosentan were also prepared by similar method (Table 3).

Table 3: Composition of Bosentan solid dispersions.

Formulation codes	Ratio of composition of solid dispersions of Bosentan			
	Bosentan	Gelucire 50/13	Poloxamer 188	Sylysia 350
Bosentan	1	-	-	-
F1	1	0.5		0.25
F2	1	1.0		0.5
F3	1	1.5		0.75
F4	1	2.0		1.0
F5	1		0.5	0.25
F6	1		1.0	0.5
F7	1		1.5	0.75
F8	1		2.0	1.0

Solubility measurement of solid dispersions

Solubility of bosentan and its solid dispersions was determined (Hecq *et al.*, 2005). An excess amount of bosentan, solid dispersions were added to 20 mL of freshly prepared distilled water in clean vials with continuous shaking on a Remi mini rotary shaker-12R-DX at 25 ± 0.5 °C for 24 h to achieve equilibrium. The filtered solutions were suitably diluted and analyzed spectrophotometrically. The results are shown in Table 4.

Table 4: Solubility, Flowability and Compressibility data of solid dispersions of Bosentan.

Formulations	Solubility (µg/mL)	Angle of repose (^{0})*	Compressibility index (%) *	Hausener's ratio*
Bosentan	12 ± 1	43 ± 2.3	31 ± 2.9	1.36 ± 0.3
F1	23 ± 2.5	24 ± 1.4	17 ± 0.9	1.12 ± 0.4
F2	54 ± 3	26 ± 2.1	19 ± 1.6	1.32 ±0.2
F3	88 ± 4	24 ± 0.4	18 ± 1.2	1.23 ±0.6
F4	99 ± 3	24 ±0.9	16 ± 1.2	1.19 ±0.5
F5	44 ± 4	25 ± 3.2	18 ± 2.7	1.18 ± 0.3
F6	76 ± 6	22 ± 2.1	19 ± 1.3	1.23 ±0.3
F7	103 ± 7	23 ± 1.4	18 ± 1.2	1.24 ±0.6
F8	127 ± 8	24 ±1.7	16 ± 1.3	1.17 ±0.5

* Mean ± SD, n=6

Flowability and compressibility measurement

Solid dispersions were characterized for flow and compressibility by measuring Compressibility index (%), Hausner's ratio (H.R) and angle of repose (Θ) (Wells and Aulton, 2007). The results are shown in Table 4.

The Hausner's ratio is a number that is correlated to the flowability of powder. The Hausner's ratio is determined by following formula;

$$Hausner's\ Ratio = \frac{Tapped\ Density}{Bulk\ Density} \quad (3)$$

Compressibility index (CI) was determined according to the formula

$$C.I = \frac{(Tapped\ Density - Bulk\ Density)}{Tapped\ Density} \times 100 \quad (4)$$

Angle of repose was determined by allowing the solid dispersions to flow through a funnel (with a 10 mm orifice diameter) and measuring the angle between the horizontal and the slope of the heap of solid dispersions. The radius (r) and height (H) of the pile were measured. Then the angle of repose (θ) was calculated using following formula.

$$\theta = tan^{-1}\ {}^{h}/_{r} \quad (5)$$

Preparation of Immediate Release (IR) Tablet

Both gelucire 50/13 and poloxamer 188 based soild dispersions were compressed on a multistation tablet machine with a punch of 8 mm diameter to produce bosentan IR tablet. The composition is shown in Table 5.

Table 5: Composition of IR tablets.

Formulation (mg/tablet)	Composition of solid dispersion (F3 and F7)				SSG	Total weight
	Bosentan	Gelucire 50/13	Poloxamer 188	Sylysia 350		
F9	62.5	93.5	-	47	5	208
F10	62.5	93.5	-	47	10	213
F11	62.5	93.5	-	47	15	218
F12	62.5		93.5	47	5	208
F13	62.5	-	93.5	47	10	213
F14	62.5	-	93.5	47	15	218

Quality Control tests for tablets

The prepared tablets were subjected to standard quality control tests. Weight variation was determined by weighing 20 tablets individually, the average weight was calculated and the percentage variation of each tablet was determined. Hardness was determined by testing 6 tablets from each formulation using a Electrolab digital portable hardness tester EH-01 (Electrolab, India) and the average applied pressure (kg/cm^2) required to crush each tablet was determined. Friability was determined by firstly weighing 10 tablets then placing them in a friability tester EF-2W (Electrolab, India) which was rotated for 4 min at 25 rpm. After dusting, the total remaining weight of the tablets was recorded and the percentage of friability was calculated. The disintegration time for the tablets was determined in 900 mL of distilled water using a programmable tablet disintegration tester ED-2L (Electrolab, India).

***In-vitro* dissolution test**

The release of bosentan from gelucire 50/13 (F9-F11) and poloxamer 188 (F12-F14) based IR tablets was determined using USP paddle type Dissolution Tester at 50 rpm. Dissolution was examined using 900 mL of simulated intestinal fluid (SIF) without enzyme. The temperature was maintained at 37 ± 0.2°C. Samples each containing 5 mL were withdrawn at 5, 10, 15, 30, 45 and 60 min intervals, filtered through a Whatman filter of 0.45 µm and replaced with an equal amount of fresh dissolution medium to maintain sink condition. Samples were then suitably diluted and analyzed spectrophotometrically at 222 nm. The dissolution studies were conducted in triplicate**.** The dissolution profiles were evaluated for amount of drug released in initial 15 min (Q_{15} min) and time taken to release 50% of the drug (T_{50}).

Dissolution Efficiency

The percent dissolution efficiency (% DE) was computed to compare the relative performance of various formulations. The % DE of a pharmaceutical dosage form is defined as the area under the dissolution curve up to a certain time, *t*, expressed as a percentage of the area of the rectangle described by 100% dissolution at the same time (Khan *et al.*, 1975). The % DE can be calculated from the following equation

$$\%\ DE = \frac{\int_0^t Y dt}{Y_{100} t} \quad (6)$$

Where, *Y* is the percent drug dissolved at time *t*.

Mean Dissolution Time

To understand the extent of bosentan dissolution rate enhancement from its formulations, the dissolution data were used to calculate the mean dissolution time (MDT) (Arias *et al.*, 1996). The MDT can be calculated by using following equation.

$$MDT_{in\ vitro} = \frac{\sum_{i=1}^{n} T_{mid}\,\Delta M}{\sum_{i=1}^{n} \Delta M} \quad (7)$$

Where, i is the dissolution sample number, n is the number of dissolution sampling times, T_{mid} is the midpoint between times T_i and T_{i-1}, and ΔM is the amount of bosentan dissolved between times T_i and T_{i-1}.

Hixson Crowell Cube root law

Finally Hixson and Crowell's cubic root law of dissolution was applied to evaluate the effect of change in surface area on dissolution rate of all the formulations. The dissolution data of Bosentan and IR tablets (F9-F14) were analyzed as per Hixson-Crowell's cube root equation. Hixson-Crowell introduced the concept of changing surface area during dissolution and derived the "cube-root law" to nullify the effect of changing surface area and to linearize the dissolution curves. Hixson-Crowell's cube root law is given by the following equation.

$$(W_0)^{1/3} - (W_t)^{1/3} = Kt \quad (8)$$

Where W_0 is initial mass and W_t is the mass remained at time '*t*', K is Hixson crowell cube root constant.

RESULTS and DISCUSSION

Phase solubility study

In case of gelucire 50/13 and poloxamer 188 when the concentration of carrier was increased above 10% W/V and 1 % w/V respectively it resulted in the formation of a gel due to higher

viscosity of solution which was not suitable for phase solubility study. The phase-solubility diagram investigated in distilled water was linear with respect to the increased weight fraction of the gelucire 50/13 (0.1-10 % *w/v*) and poloxamer 188 (0.1 to 1 % *w/v*) indicating the solvent properties of both carriers for bosentan, giving A_L type solubility. The values of the stability constant depend on slope values. The greater the value of the slope, greater is the capacity of the polymer to solubilize. The slope value for gelucire 50/13 and poloxamer 188 was found to be 0.254 and 0.335 respectively. Higher slope value for poloxamer 188 suggests that it has better capacity to solubilize the drug. The Gibbs free energy $\Delta G_{tr}°$ values were all negative for gelucire 50/13 and poloxamer 188 at various concentrations (Table 1-2), indicating the spontaneous nature of solubilization (Mura *et al.*, 1996). Gibbs free energy decreased with increase in concentration of gelucire 50/13 and poloxamer 188 demonstrating that the reaction became more favorable as the concentration of both carriers increased. Increased solubility may be due to the improved wettability of the bosentan particles in aqueous solution of gelucire 50/13 and poloxamer 188. These results agreed with the well-established formation of soluble complexes between the water-soluble polymeric carriers like gelucire 50/13 and poloxamer 188 with poorly water-soluble drugs (Trapani *et al.*, 1999).

FT-IR spectroscopy studies

Infrared spectra of bosentan and its 1:1 solid dispersion with gelucire 50/13 and poloxamer 188 are presented in Figure 1. Bosentan alone showed –OH monomeric stretching at 3630 cm^{-1}, -CH stretching of aromatic rings in the range of 3000-3100 cm^{-1}, secondary –C-O stretching at 1170 cm^{-1} and primary –C-O stretching at 1072 cm^{-1} which remained unchanged in case of formulations with both gelucire 50/13 and poloxamer 188, indicating no interaction between bosentan-gelucire 50/13 and bosentan-poloxamer 188.

Differential scanning Calorimetry (DSC)

Figure 2 represents the DSC thermograms of bosentan and its 1:1 solid dispersion with gelucire 50/13 and poloxamer 188. The DSC thermogram of bosentan exhibited a sharp endothermic peak at 104.9 °C *(T_{fus})*, and latent heat of fusion *(ΔH_{fus})* 267.7 mJ. The endothermic peak indicated the crystalline nature of the drug whereas the DSC thermogram of its 1:1 formulation with gelucire 50/13 exhibited a slightly broad endothermic peak at 105.2 °C. This formulation exhibited decreased latent heat of fusion 52.9 mJ. Similarly the DSC thermogram of its 1:1 solid dispersion with poloxamer 188 exhibited a slightly broad endothermic peak at 106.4^0C with decreased latent of fusion 80.1 mJ. Lower value of latent heat of fusion *(ΔH_{fus})* 8.9 mJ for both carriers clearly indicated the formation of solid dispersion and the drug is in the amorphous state. This also suggested that the drug might have formed complex with the carrier during thermal analysis (Damian *et al.*, 2002). The DSC thermogram of formulations exhibited no shift in peaks indicating both the carriers are compatible with bosentan.

Solubility

Solubility data of bosentan and its solid dispersion with gelucire 50/13 and poloxamer 188 in distilled water suggests more than eightfold and tenfold increase in solubility of the bosentan respectively (Table 4). The solubility of bosentan increased with increase in the ratio of gelucire 50/13 and poloxamer 188. The improved solubility of bosentan in gelucire 50/13 solid dispersions can be explained by the improved wettability of the bosentan particles, and improved surfactive power (Potluri *et al.*, 2011). Whereas the improved solubility of bosentan from poloxamer 188 based solid dispersions could possibly be because of the combined action of the surface activity, solubilization and wetting effect of poloxamer 188 (Karekar *et al.*, 2009).

Flowability and compressibility

The values of angle of repose (43°), C.I (31 %) and H.R (1.36) for pure drug bosentan revealed that it is a poorly flowable drug. Whereas flowability and compressibility of solid dispersion formulations (both gelucire 50/13 and poloxamer 188) were within the theoretical range for processing into tablet dosage form (Table 4). Addition of Sylysia 350 (50 % of the quantity of gelucire 50/13 or poloxamer 188) in each solid dispersion formulations was found to be the optimum quantity for converting the waxy solid dispersions into freely flowable powders which can be processed into a tablet. This could be attributed to high oil adsorption capacity and high specific surface area of sylysia 350 (Bahl *et al.*, 2008).

Evaluation of immediate release tablets of bosentan

Drug content values (94-99%) ensured uniform mixing of bosentan, gelucire 50/13 or poloxamer 188 and Sylysia 350. Hardness of the tablets was in the range of 4.9 kg/cm^2 to 5.4 kg/cm^2. This revealed that the required compressibility was imparted by sylysia 350. Gelucire 50/13 and poloxamer 188 are waxy materials and tend to stick to the punches during compression. This problem was also resolved by uniform mixing with sylysia 350. Friability values were in the range of 0.37% and 0.44%, which ensured no loss of material from the surface or edge of tablets. This may be attributed to the waxy nature of gelucire 50/13 and poloamer 188. All the formulations passed weight variation test which was an indication of good flowability. Formulation F11 and F14 showed a disintegration time of 7 and 9 min respectively. SSG produced quick disintegration because of rapid water penetration and subsequent swelling (Zimmer *et al.*, 2015). The results of evaluation tests are summarized in Table 6.

Table 6: Quality Control Tests of Bosentan IR Tablets.

Formulation code	Hardness (Kg/cm^2)*	D.T. (min)*	Friability (%)*	Weight Variation	Drug Content (%)*
F9	4.9 ± 0.27	28 ± 2	0.41	PASS	95.8±0.67
F10	5.3 ± 0.76	013±2	0.44	PASS	97.9±0.99
F11	5.1 ± 0.23	07 ± 1	0.39	PASS	98.4±0.27
F12	5.1± 0.26	32 ± 3	0.35	PASS	96.9±0.61
F13	5.4 ± 0.37	12 ± 3	0.37	PASS	97.2±0.87
F14	4.9 ± 0.16	09 ± 1	0.42	PASS	96.5±0.14

* Mean ± SD, n=6.

***In vitro* dissolution test**

The dissolution profile of bosentan is very poor as around 15% of drug was dissolved in 1 h whereas gelucire 50/13 soild dispersion based IR tablets (F9 to F11) exhibited more than 90 % drug dissolution in 1 h. The observed enhancement may be attributed to the effects of solid dispersion and surface adsorption. Gelucire 50/13 has an HLB value of 13 and is expected to solubilize the hydrophobic drug bosentan in solid state (Chella and Tadikonda, 2015). Simultaneous presence of Sylysia 350 increased the effective surface area over which the drug is spread leading to rapid desorption of drug with exposure to dissolution medium (Planisek *et al.*, 2011).

The results are shown in Figure 3. Similarly poloxamer 188 solid dispersion based IR tablets (F12 to F14) also exhibited more than 90 % drug dissolution with in 1 h. This may attributed to the following reasons such as HLB value 29, molecular dispersion of drug in polymer chain, formation of glassy solution which resulted in quick dissolution upon contact with dissolution medium (Song *et al.*, 2016). The results are shown in Figure 4.

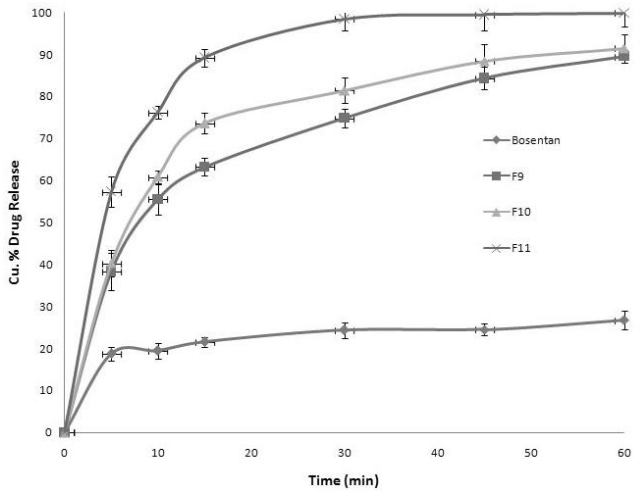

Fig. 3: *In vitro* dissolution profile of bosentan and gelucire 50/13 immediate release tablets (F9-F11).

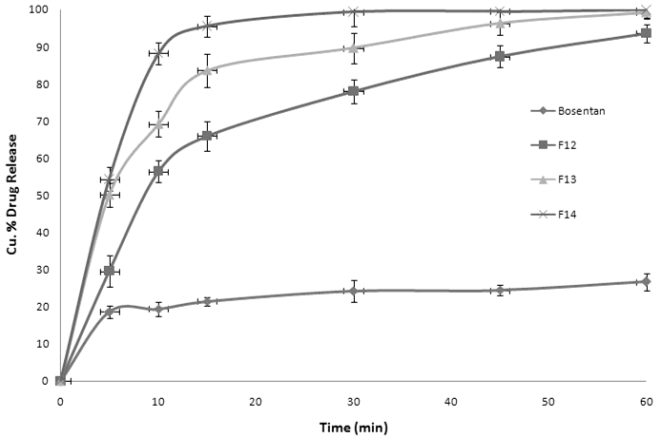

Fig. 4: *In vitro* dissolution profile of bosentan and poloxamer 188 immediate release tablets (F12-F14).

The DE_{15} value for each formulation is presented in Table 7. The DE_{15} value for bosentan was significantly lower than tablets. Dissolution onset of F11 and F14 was very fast and among the tablet formulations (F9 to F14). Formulation F11 and F14 showed very high dissolution efficiency values 89 and 95 respectively. This can be attributed to quick disintegration of IR tablets. The *MDT* for bosentan was 19.41 min and it decreased to 9.25 and 8.33 min for F11 and F14 respectively. This suggested that dissolution of bosentan from these two formulations was faster compared to other formulations**.** Q_{15} values for formulation F11 and F14 showed more than 4 fold increase in dissolution rate. Similarly T_{50} values for F11 and F14 showed that it took less than 5 min to dissolve 50% of bosentan. Correlation coefficient for Hixson Crowell's equation was higher for all formulations suggesting that the rate of dissolution increased with increase in surface area.

Table 7: Dissolution parameters of Bosentan and IR tablet formulations (F9 to F14).

Formulation	% DE_{15}	MDT (min)	Q_{15}	T_{50} (min)	Hixson Crowell's cube root constant (r^2)
Bosentan	21	14.41	21.5	*	0.913
F9	63	14.08	63.2	10	0.972
F10	73	10.73	73.6	10	0.983
F11	89	9.25	89.2	5	0.991
F12	66	15.24	66	10	0.967
F13	83	11.86	83.6	5	0.995
F14	95	8.33	95	5	0.996

% DE_{15} is the percent dissolution efficiency at 15 min and MDT is the mean dissolution time in min, *50 % of drug was not dissolved within 1 h of dissolution study.

CONCLUSION

Hence from the above research work, it may be concluded that both gelucire 50/13 and poloxamer 188 can be used to enhance the dissolution of a poorly water soluble drug bosentan. Gelucire 50/13 and poloxamer 188 plays a significant role in enhancement of drug solubility and dissolution. The surface adsorbent, sylysia 350 may be used to impart good flow and compressibility to solid dispersions. Among the two carriers, poloxamer 188 exhibited better solubility and dissolution enhancement potential.

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