ORIGINAL ARTICLE

Formulation and Evaluation of Bosentan Solid Dispersion

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Abstract

Aim: The therapeutic efficiency of a formulation will depend on various crucial parameters such as solubility of the drug, stability of the compound, excipients used in the formulation of finished dosage form, and the manufacturing technology used for the fabrication of finished dosage form. This research work is an attempt to enhance the solubility and dissolution rate by fabricating solid dispersion (SD) of the bosentan using hydrophilic polymers, soluplus, and kollidon VA 64. SDs of different drug: Polymer ratios were prepared using both the polymers separately (1:1, 1:2, 1:3, and 1:4). The SDs obtained were characterized by differential scanning calorimetry and X-ray powder diffraction analysis. **Material and Methods:** Bosentan, soluplus, and kollidon VA 64 were the important materials and hot-melt extrusion (HME) is the equipment used for manufacturing of SD. **Results and Discussion:** The studies shown that the crystalline drug was successfully converted to amorphous form by fabricating SD using HME. The SDs were further evaluated by performing dissolution studies, and a comparison was made between the pure drug and the SDs. The SD showing better release profile in water as dissolution medium was further evaluated. SD2 shown marked increase in the dissolution rate when compared with the pure drug dissolution. **Conclusion:** SD fabricated using soluplus as a polymer shown better release profile when compared with SDs fabricated with kollidon VA 64.

Key words: Hot-melt extrusion, polymer, differential scanning calorimetry, X-ray powder diffraction, bosentan monohydrate, soluplus, kollidon VA 64

INTRODUCTION

Drug solubility, absorption, and reproducible bioavailability are recognized today as few of the major challenges in oral delivery of new drug substance. Drug substances, for which solubility enhancement can improve the oral bioavailability, are substances that are classified in Class II (poor solubility/high permeability), and Class IV (poor solubility/poor permeability). Formulation a poorly soluble compound to a finished dosage is a challenge task because of its less solubility and dissolution. To enhance the solubility of those drugs different techniques such as modification of crystal habits, micronization, usage of surfactants, complexation, co-solvents, and solid dispersion (SD). This SD can be fabricated by different techniques such as spray drying, solvent evaporation, melt fusion, and hot-melt extrusion (HME) technique. Of the different techniques mentioned HME is the one which is having a very good industrial feasibility and there won't be any usage of solvents during the manufacturing of SD. The ultimate objective of any research was done in the field of pharmaceuticals id to serve the society's need by developing highly efficient formulations. The term SD refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The drug was molecularly dispersed in amorphous particles.[1-4]

Bosentan belongs to the class of organic compounds known as bipyrimidines and oligopyrimidines. These are organic compounds containing two or more pyrimidine rings directly

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linked to each other. Pyrimidine is a 6-membered ring consisting of four carbon atoms and two nitrogen centers at the 1- and 3- ring positions bosentan belongs to a class of drugs known as endothelin receptor antagonists. Patients with PAH have elevated levels of endothelin, a potent blood vessel constrictor, in their plasma and lung tissue. Bosentan blocks the binding of endothelin to its receptors, thereby negating endothelin's deleterious effects. Bosentan is metabolized in the liver by the cytochrome P450 enzymes CYP2C9 and CYP3A4 (possibly CYP2C19), producing three metabolites, one of which, Ro 48-5033, is pharmacologically active and may contribute 10-20% to the total activity of the parent compound. Poorly soluble in water (1.0 mg/100 ml) and in aqueous solutions at low pH (0.1 mg/100 ml at pH 1.1 and 4.0; 0.2 mg/100 ml at pH 5.0). Solubility increases at higher pH values (43 mg/100 ml at pH 7.5).[5]

This research involves usage of HME in the fabrication of SD using a BCS Class II compound and hydrophilic polymers and to evaluate the industrial scale applicability of the HME process.

The aim of this study is to prepare SD by HME technique and to evaluate the SD, by formulating finished dosage form with the SD prepared using hot-melt extruder and the formulation showing better release profiles was further evaluated in comparison with the batch fabricated with active pharmaceutical ingredient (API).

Table 1: Composition of Bosentan solid dispersions

Formulation code	Composition of solid dispersions	Drug: Polymer ratio
SD1	Bosentan: Soluplus	1:1
SD2	Bosentan: Soluplus	1:2
SD3	Bosentan: Soluplus	1:3
SD4	Bosentan: Soluplus	1:4
SD5	Bosentan: Kollidon VA64	1:1
SD6	Bosentan: Kollidon VA64	1:2
SD7	Bosentan: Kollidon VA64	1:3
SD8	Bosentan: Kollidon VA64	1:4

The objective of this study is first to enhance the rate and extent of dissolution of model drug by SD technique and to study solid state, drug carrier interactions and to prevent re crystallization of drug from SDs.

MATERIALS AND METHODS

Bosentan is the free sample provided by matrix API team. The polymers used in the HME process soluplus and kollidon VA 64 were the free samples provided by BASF. The active pharmaceutical ingredient and the polymers used in the manufacturing of the SD are of standard quality complying to official monographs. All the chemicals used for the analysis are laboratory grade complying to official standards.

Preparation of bosentan SD

Preparation of SD by hot-melt extrusion technique

The carriers used in the study were soluplus and kollidon VA64 in the preparation of SD by HME method. SDs were prepared in bosentan: Soluplus and bosentan: Kollidon VA64 with ratio 1:1, 1:2, 1:3, and 1:4. Bosentan is initially mixed with soluplus and kollidon VA64 separately. The following temperatures were maintained in hot-melt extruder during the extrusion process (Table 1).[6]

Extrusion parameters of SDs

The drug and carrier blend was added to the feeding zone slowly. The formed extrudes were collected and milled through 40G screen using Quadracomill. The milled material was passed through sieve no. 60 (ASTM). The obtained SDs were characterized for solubility studies (Table 2).

Characterization of SDs[7]

The solid state properties of drug in the SD was investigated using different methods

Table 2: Hot melt extruder - processing parameters

Formulation	Temperature in different zones (°C)				Screw speed (rpm)
	Zone 1	Zone 2	Zone 3	Zone 4	
SD1	70	80	90	100	100
SD2	70	80	90	100	100
SD3	70	80	90	100	100
SD4	70	80	90	100	100
SD5	70	80	90	100	100
SD6	70	80	90	100	100
SD7	70	80	90	100	100
SD8	70	80	90	100	100

Differential scanning calorimetry (DSC)

Thermal properties of drug, polymer, and SD were investigated using a METTLER differential scanning calorimeter thermal analysis controller with an intracooler-2 cooling. About 3-5 mg of product was placed in perforated aluminum sealed 50 µl pans, and the heat runs for each sample was set from 25°C to 250°C at 20°C/min, under an inert environment using nitrogen. The apparatus was calibrated using pure metals like indium with known melting points and heat of fusion (ΔH fusion).

Crystalline state and particle morphology X-ray powder diffraction (PXRD)

The physical state of drug in the different samples was evaluated by PXRD. Diffraction patterns were analyzed by XRD model d8 advanced A17-B60 by Bruker Instruments. The pattern was collected with a tube voltage of 30 kV and a tube current of 15mA of in step scan mode (4°/min). A chemo metric method was used to evaluate the X-ray results. The self-modeling curve resolution (SMCR) method is a chemo metric procedure used for two and three component systems to deconvolve raw spectroscopic data and to obtain an analytical solution in band form, which provides a clearer interpretation. A computer program involving the use of SMCR and multivariate curve resolution methods was employed to analyze the XRPD data and to study the conversion of crystalline drug to amorphous form and interactions between drug and the excipients in the formulated SDs.

In vitro dissolution studies[8-10]

A dissolution study was conducted for API and SDs using the United States Pharmacopeia type-II apparatus (ELECTROLAB). The dissolution test was performed using 900 mL of water and 0.5% sodium lauryl sulfate (SLS) in water as the dissolution medium at 50 rpm and at a temperature of 37°C ± 0.5°C. 10 ml of aliquots were periodically withdrawn, and the sample volume was replaced with an equal volume of fresh dissolution medium. The samples were diluted and analyzed spectrophotometrically at 221 nm (Table 3).

Table 3: *In vitro* dissolution study parameters

Parameter	Details
Dissolution apparatus	Type II (USP)
Volume	900 mL
Rotations per minute (rpm)	50
Temperature	37+0.5°C
Medium	1. Water 2. 0.5% SLS in water
Sample volume withdrawn	5 ml
Time periods	10, 15, 30, 45, and 60 min
Wave length	221 nm

Drug content estimation

About 10 mg of pure drug was taken into 100 ml volumetric flask and dissolved this was diluted to volume with diluent and shaked. 10 ml of this solution was taken into a 100 ml volumetric flask and diluted to volume with diluent. The solution was filtered through 0.45 µm nylon or 0.45 µm PVDF membrane filter. Drug content was analyzed against blank by UV spectrophotometer at 221 nm. SDs equivalent to 10 mg of drug was transferred to a separate 100 ml volumetric flask and about 75 ml of diluent was added and Sonicated for 20 min with intermediate shaking and diluted to volume with diluent and mixed well. The solution was filtered through 0.45 µm nylon or 0.45 µm PVDF membrane filter and drug content was analyzed against blank by UV spectrophotometer at 221 nm.

RESULTS AND DISCUSSION

This study was undertaken to formulate SDs bosentan with hydrophilic polymers, soluplus, and kollidon VA 64 by employing HME technique. This study involves characterization of SDs and to perform the dissolution studies of SDs in comparison with the pure drug.

Results and discussion of the above studies are presented below:

DSC

Polymorphic studies were performed by DSC for API. The melting range of API was found to be 107°C to 134°C. The sharp peak in the thermogram of API indicates crystalline nature of drug and no other polymorphs were found shown in Figure 1. The sharp peaks in the thermogram of model drug indicate crystalline nature of drug and SDs have no sharp peaks which indicate their amorphous nature. This was further supported by PXRD, as shown in Figure 2 and 3. The sharp peaks in the thermogram of model drug indicate crystalline nature of drug and SDs have no sharp peaks which indicate their amorphous nature. This was further supported by PXRD, as shown in Figure 3.

PXRD

The X-ray diffractogram of the model drug has sharp peaks at diffraction angles (2θ) showing a typical crystalline pattern. The XRD patterns of the model drug showed sharp peaks at 8.65°, 12.76°, 18.77°, 19.73°, 20.03°, 20.70°, 22.74°, 26.12°, 28.24°, 31.14°, and 31.99° (2θ), indicating the crystalline nature of model drug, Figure 4. The sharp drug peaks were not

observed in the SDs indicating that the drug was completely converted into amorphous nature, Figures 5 and 6.

In vitro drug release

The SDs fabricated (SD1, SD2, SD3, SD4, SD5, SD6, SD7, and SD8) were subjected to dissolution studies, water as the dissolution medium and comparison were made between the pure drug and SDs (SD1-SD8) dissolution data. SD2 batch fabricated with soluplus as the polymer showing a profound increase in the rate and extent of dissolution when compared with the API dissolution, *in vitro* release profiles were shown in Table 4 and Figure 7. SD2 and the pure drug was further evaluated in 0.5% SLS as the medium for the dissolution studies. The results of SD2 shown better release profile in comparison with the pure Drug, *in vitro* release profiles were shown in Table 5 and Figure 8.

Characterization of bosentan monohydrate API [Figure 1]

The sharp peak in the thermogram of API indicates crystalline nature of drug and no other polymorphs were found.

Characterization of SDS [Figure 3 and 4]

DSC's of the solid dispersions was assigned figure 2 and 3.

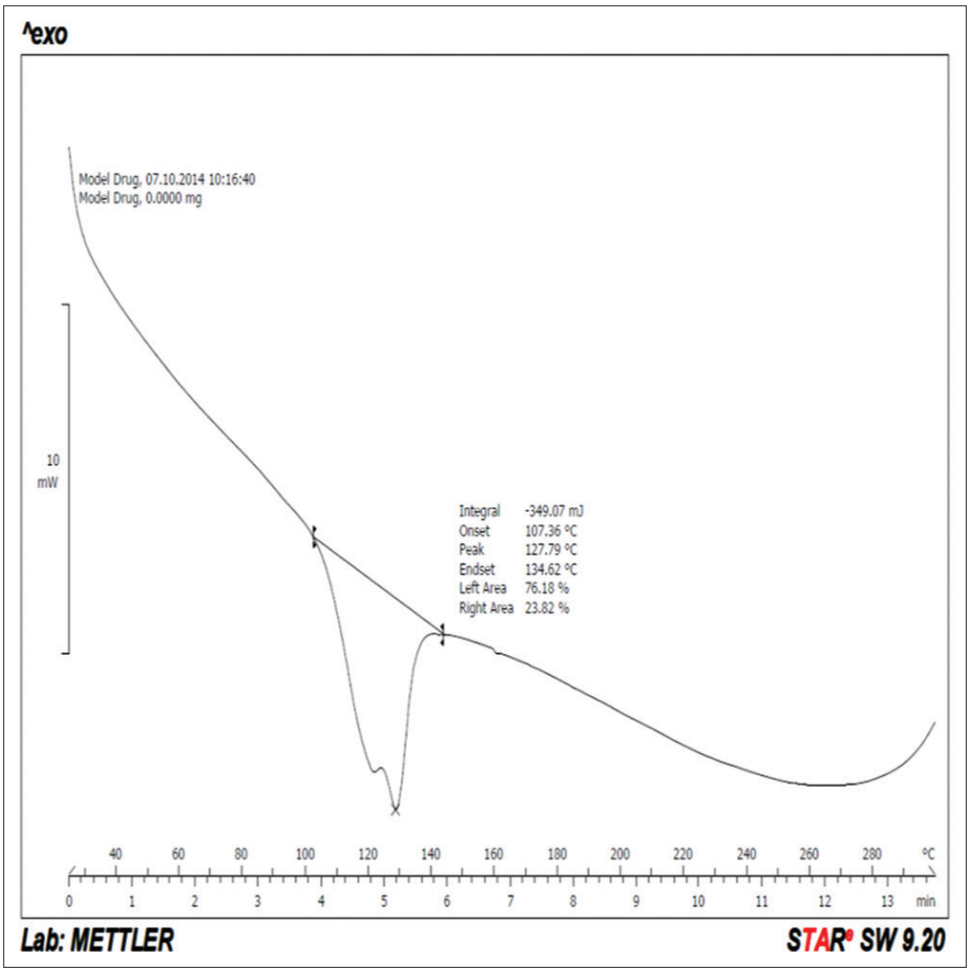

Figure 1: Differential scanning calorimetry thermogram of bosentan monohydrate

Table 4: *In-vitro* dissolution studies of the pure drug and solid dispersion in water as dissolution medium

Time period (min)	Pure drug	% Drug release							
		SD1	SD2	SD3	SD4	SD5	SD6	SD7	SD8
15	7.37	28.3	43.27	25.5	22.6	15.16	25.4	21.31	20.28
30	14.14	34.2	63.92	44.48	26.48	17.49	38.29	27.17	26.48
45	22.6	40.35	77.57	54.46	45.7	26.22	40.59	37.5	30
60	25.13	46.62	94.7	64.02	54.42	35.14	50.81	48.6	38.1

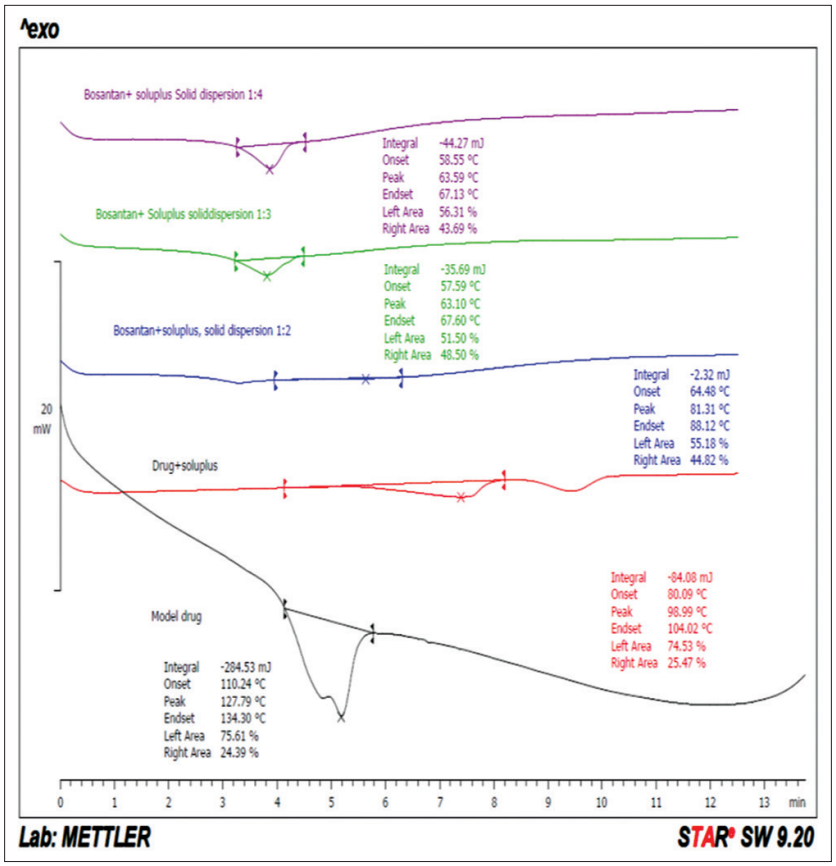

Figure 2: Differential scanning calorimetry thermogram of bosentan monohydrate active pharmaceutical ingredient, bosentan, and soluplus physical mixture, SD1, SD2, SD3, and SD4 overlay

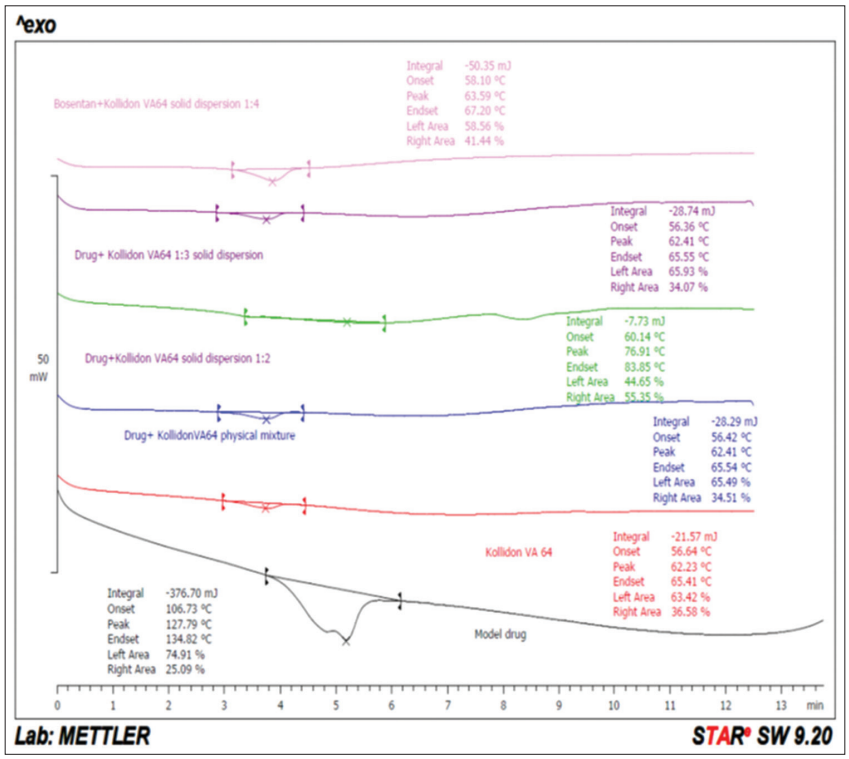

Figure 3: Differential scanning calorimetry thermograms of bosentan monohydrate active pharmaceutical ingredient, bosentan, and kollidon VA 64 physical mixtur, SD5, SD6, SD7, SD8 overlay

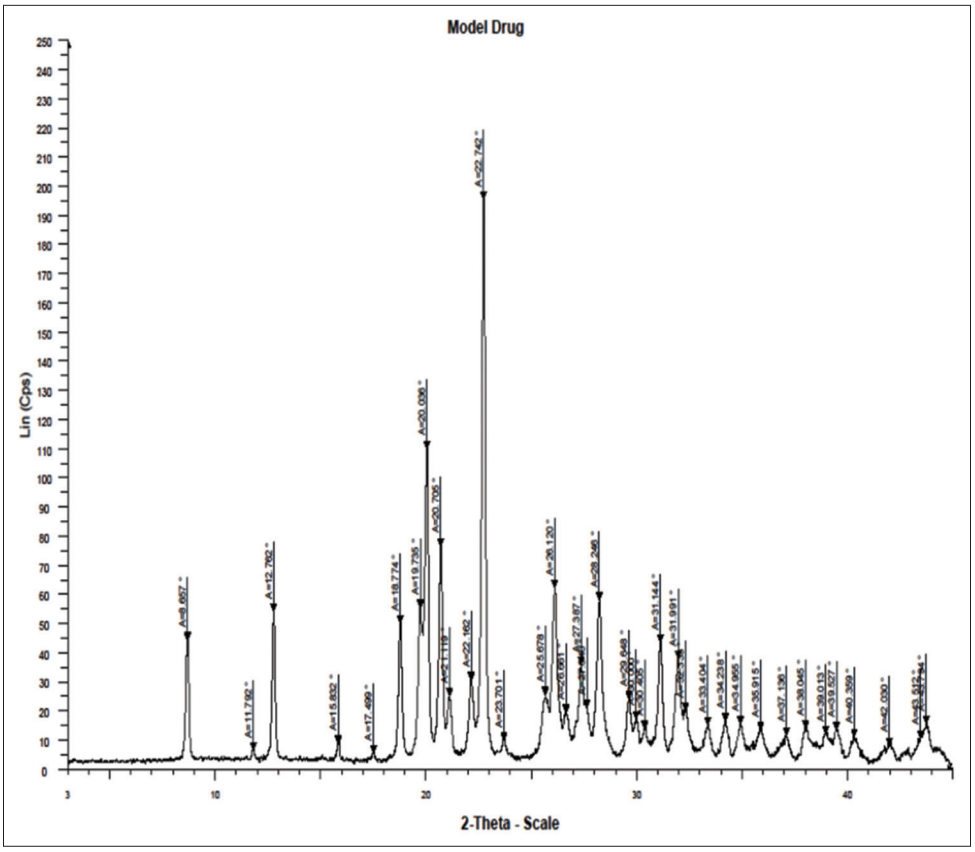

Figure 4: Powder X-ray diffraction study of bosentan monohydrate

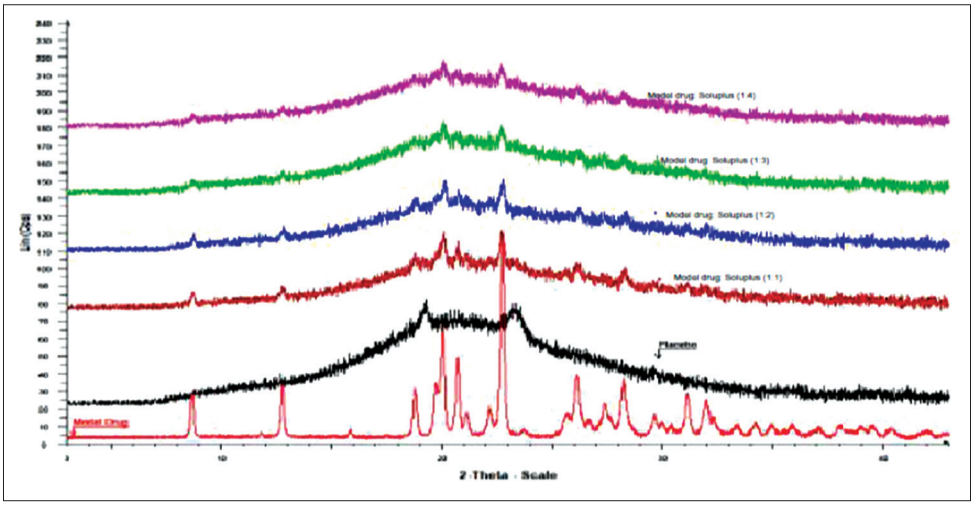

Figure 5: X-ray powder diffraction data of bosentan monohydrate active pharmaceutical ingredient, placebo, bosentan, and soluplus physical mixture SD1, SD2, SD3, SD4 overlay

Table 5: *In-vitro* dissolution studies of the pure drug and solid dispersion (SD2) in 0.5% SLS in water as dissolution medium

Time (min)	% Drug release	
	Pure drug	SD2
15	50.48	93.80
30	54.20	94.40
45	62.00	96.40
60	68.48	101.32

Characterization of SDS [Figure 2 and 3]

The sharp peaks in the thermogram of model drug indicates crystalline nature of drug and solid dispersions have no sharp peaks which indicates their amorphous nature. This was further supported by PXRD.

Data of PXRD diffractograms [Figure 5 and 6]

The sharp drug peaks were not observed in the solid dispersions indicating that the drug was completely converted into amorphous nature.

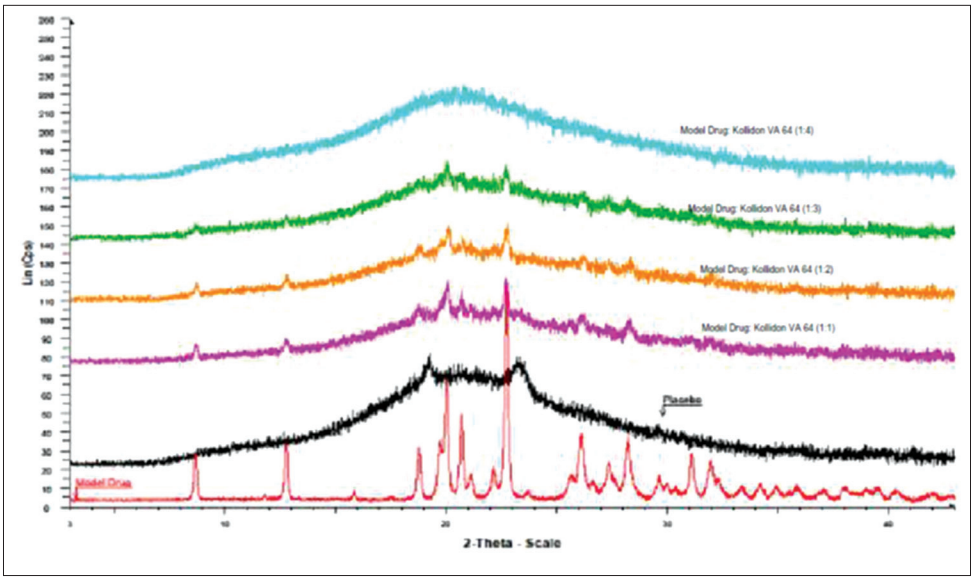

Figure 6: X-ray powder diffraction data of X-ray powder diffraction data of bosentan monohydrate active pharmaceutical ingredient, placebo, bosentan, and kollidon VA 64 physical mixture SD5, SD6, SD7, SD8 overlay

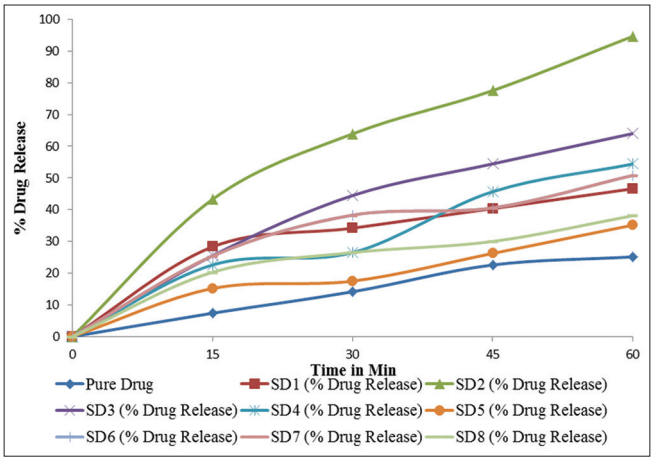

Figure 7: Comparison of dissolution profile of different solid dispersions in water

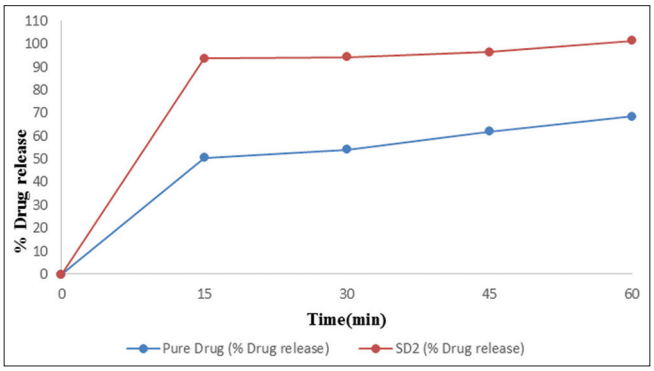

Figure 8: Comparison of dissolution profile of model drug and optimized solid dispersion in 0.5% sodium lauryl sulfate in water

CONCLUSION

The main objective of this study is to fabricate the SD of bosentan with hydrophilic polymers, soluplus, and kollidon VA 64 by HME technique. The obtained SD was evaluated by DSC and PXRD for confirming the conversion of crystalline API to amorphous form; the results of DSC and PXRD shown successful conversion of API in to amorphous form and the *in vitro* dissolution studies of SD2 shown marked increase in the rate and extent of drug release.

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