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Research Article

NOVEL TECHNIQUES TO PREPARE SOLID DISPERSIONS TO IMPROVE SOLUBILITY OF BOSENTAN

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ABSTRACT

Objective: *Bosentan presents challenges with regard to low and variable oral bioavailability due to its poor aqueous solubility and poor dissolution in gastric fluid. Solid dispersion has been used as the solubility enhancement technique due to its ability to develop suitable system with improved solubility and dissolution rate.* ***Methods:*** *Solid dispersions of bosentan were prepared by using novel techniques like solvent controlled coprecipitation, fusion and nanoprecipitation. Polymers with different ionic characteristics like Eudragit® EPO (cationic), Eudragit® L 100 55 (anionic) and Povidone K 30 (non-ionic) were employed at three different ratios of 1:1, 1:2 and 1:3 to prepare the solid dispersions of weakly basic bosentan. Dissolution study in buffers corresponding to different physiologically relevant pH was performed to understand the effectiveness of the technique and effect of the polymer. Additionally, samples were subjected for X-ray* ***powder*** *diffraction study to understand the nature of the drug in solid state in the solid dispersion systems.* ***Results:*** *It was observed that irrespective of the pH of the dissolution media, the dissolution rate of the solid dispersions of BOS prepared with Eudragit® L 100 55 are higher than that of pure drug and the solid dispersions prepared with the other polymers i.e. Eudragit® EPO and Povidone K 30, which is attributed to the weakly basic nature of bosentan. The diffractograms show decrease in the crystallinity of bosentan in the solid dispersions.* ***Conclusion:*** *The combination of solid dispersion technology with supersaturable systems appears to hold promise for improving dissolution and bioavailability of poorly soluble drugs. The selection of polymers that can inhibit crystallization of the drug in a supersaturated state becomes the key factor for an effective formulation. The present work is an attempt in this direction.*

KEYWORDS*: Solid Dispersion, Super Saturable systems, Insoluble drugs.*

INTRODUCTION

Water insolubility has always been a key obstacle in pharmaceutical formulations, affecting formulation stability and drug bioavailability. In the pharmaceutical industry, there is general consensus that poorly water-soluble drug candidates are becoming more prevalent [1]. It is estimated that approximately 40% of active substances which are poorly soluble in water are being identified through different combinatorial screening programs and high throughput screening [2, 3]. In the process of absorption of a drug candidate with reasonable membrane permeability, the rate-limiting step is the drug dissolution step. A compound that is poorly soluble is defined as the one dissolving in less than 1 part per 1000 parts of water and when water-solubility is less than 1µg/mL, which is often the case for contemporary drug candidates. For such drugs, the oral bioavailability from conventional formulations may be unacceptable.

Many formulation strategies have been reported to improve the solubility and bioavailability of poorly-soluble compounds. However, when routine solubility enhancing techniques like co-solvent addition, pH modification, heat application, particle size reduction etc. fail to resolve solubility issues; some advanced formulation strategies are approached to improve the solubility of poorly soluble drugs. These include complexation with cyclodextrins [4, 5], polymeric nanoarchitecture [6], self-emulsifying drug delivery system [7], emulsions and microemulsion, nano suspensions, micellar solubilization and solid dispersion [8].

The formulation development of poorly soluble drugs by solid dispersion technology utilizing different polymeric carrier has been widely researched over the past four decades for solubility and related bioavailability enhancement. In-spite of the active research till date, there has not been much marketed product based on solid dispersion technology. The main reason for this being stability and scale up problems associated with this method, as reported by several authors [9]. Nonetheless, solid dispersion technique is known to be an effective approach to keep drugs stable in the solid state, thereby improving the dissolution rate and oral absorption by inhibiting reprecipitation and/or recrystallization in supersaturated system. In solid dispersion, the drug is present in the carrier matrix either in molecularly distributed form, in the form of amorphous aggregates or, small crystalline or, partially crystalline form. The amorphous state is reported to have more solubility as compared to crystalline state [8-10]. All these forms account to have rapid drug dissolution of poorly soluble drugs leading to a supersaturated state. The stabilization of this supersaturated state by preventing reprecipitation of the drug appears to be the key to improve oral absorption.

Bosentan (BOS) chemically named as (4-tert-butyl-N-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]benzene-1-sulfonamide) is a non-peptide human endothelin-I receptor antagonist which is recommended for the treatment of pulmonary arterial hypertension [11]. It is classified as BCS class-II drug demonstrating approximately 50% absolute bioavailability which might be due to poor aqueous solubility (1.0 mg/100 mL) and dissolution, resulting in its low therapeutic outcome [12].

The present work is an attempt to prepare solid dispersions of bosentan with an objective to improve its dissolution. Rapid onset of

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action is desirable to provide fast relief in the treatment of pulmonary arterial hypertension. Therefore, it is necessary to enhance the aqueous solubility and dissolution rate of BOS to obtain faster onset of action, minimize the variability in absorption and improve its overall oral bioavailability.

MATERIALS AND METHODS

Materials:

Bosentan (BOS) was received from Natco Pharma Limited, Hyderabad, India. BOS is practically water insoluble compound with a melting point around 104.9°C. The polymers: poly(methacrylic acid, ethyl acrylate) marketed under the trade name Eudragit® L 100 55 and poly(butyl methacrylate, (2-dimethylaminoethyl) methacrylate, methyl methacrylate) marketed under the trade name Eudragit® EPO were purchased from Evonik Industries whereas, Povidone K30 was supplied by DKSH India Pvt. Ltd. All the excipients were used as received. All other ingredients used were of pharmaceutical grade and solvents used were of HPLC grade. Water used in this study was purified by a Milli-Q Synthesis A10 system (Millipore, Billerica, MA) unless otherwise mentioned.

Methods:

Solubility parameter calculation:

The solubility parameter calculation was carried out by *in-silico* molecular modelling approach based on molecular dynamics. It aims to estimate the solubility for binary combinations of BOS with commonly used polymers. Solubility parameters using Van Krevelen methods, of both drug as well as the polymers were calculated in order to determine the theoretical drug/polymer miscibility [13].

Preparation of solid dispersions of BOS:

The techniques used for the preparation of the solid dispersions are fusion technique, solvent controlled coprecipitation technique and nanoprecipitation technique. In all the techniques, solid dispersions of BOS were prepared using three different polymers, Eudragit® L 100 55 (anionic), Eudragit® EPO (cationic) and Povidone K 30 (non-ionic). The ratio of drug to polymer was 1:1, 1:2 and 1:3.

Fusion technique: Required quantity of BOS and the respective polymers were mixed thoroughly in a mortar and pestle and weighed into a stainless steel container and heated initially to 80°C on oil bath and stirred continuously using a stainless steel rod until the blend softens and melts. The final temperature was about 160°C. The soft and molten mass was subjected for sudden cooling over an ice bath and then allowed to cool to room temperature (25°C±3°C). The solidified dispersions were milled approximately after 1 hour using a mixer grinder (Maple). The prepared samples were stored at 25°C in a desiccator. The resulting dried solid dispersion samples were characterized and analysed.

Solvent controlled coprecipitation technique: BOS and the polymer were dissolved in N, N- Dimethyl acetamide (DMA). The solution was introduced at ambient temperature into the respective antisolvent kept under stirring at 2500 to 3000 rpm under a laboratory stirrer by spraying through a spray nozzle 1mm in diameter with a spray rate of 12 gm per minute. The DMA-antisolvent phase ratio was maintained at 1:12 (w/w). The resulting precipitate was separated by filtration through two layer of nylon filter cloth (200 mesh followed by 400 mesh) under vacuum. The resulting precipitate was washed with 9.0 liters of the respective antisolvents. The wet precipitate mass was dried in tray dryer at 50°C for 9 hours. The resulting dried solid dispersion samples were characterized and analysed. The antisolvents used were 0.01 N HCl for Eudragit® L 100 55 containing preparation, 0.067 M Phosphate Buffer, pH 6.8 for Eudragit® EPO containing preparation and water for Povidone K 30 containing preparation.

Nanoprecipitation technique: BOS was dissolved in ethanol (98%). Eudragit® L 100 55 was dissolved in 0.067 M Phosphate Buffer, pH 6.8, Eudragit® EPO was dissolved in 0.1 N HCl and Povidone K 30 was dissolved in water. The drug solution was added to the polymer solution by spraying at a rate of 12 gm/min under stirring at 500 to 700 rpm. This resulted in a colloidal dispersion of BOS. The mean size and size distribution of dispersions was determined by photon correlation spectroscopy using Zetasizer ZS 90 (Malvern Instruments, Malvern, UK). Each sample was diluted to a suitable concentration with filtered Milli-Q water. Analysis was performed at 25°C with an angle of detection of 90°. The mean size was directly obtained from the instrument. The drug polymer complex in the colloidal dispersions was further precipitated by addition of the corresponding antisolvent. The antisolvent used was 0.01N HCl for Eudragit® L 100 55 containing preparations, 0.067 M Phosphate Buffer, pH 6.8 for Eudragit® EPO containing preparations and water with few crystals of sodium chloride (0.05% w/v) for Povidone K 30 containing preparations. The resultant wet mass was separated by centrifugation process (Kubota®, 7780 Japan) at 7000 rpm for 7 min. The wet precipitate were further separated by filtration under vacuum through two layer of nylon filter cloth (200 mesh followed by 400 mesh). The wet precipitate was dried in tray dryer at 60°C. The resulting dried solid dispersion samples were characterized and analysed.

Characterization of the solid dispersions:

The solid dispersions were evaluated for angle of repose, bulk and tap density. Carr's Index values and Hausner's ratio were calculated from bulk and tap density data. The moisture content of the solid dispersions was analyzed by Karl Fischer (K.F) titration method. The porosity (%) was determined by liquid displacement method.

BOS content in all the samples of solid dispersions was analyzed by UV spectrophotometry. Required quantity of solid dispersion was dispersed in 5 mL of ethanol. The suspension was sonicated in an ultrasonic bath for 15 minutes and then centrifuged for 15 minutes at 2500 rpm. The supernatant was filtered through Nylon 0.45µm filter (Millipore Millex-HN). The filtrate was suitably diluted and the absorbance was read at 266 nm. A standard graph was plotted by measuring the absorbance of different concentrations of BOS in ethanol (2-12 mcg/mL). The correlation coefficient (R^2) of the regression line was 0.9997. The drug concentration in the test solution was obtained from regression equation.

X-ray Powder Diffractometry (XRPD):

XRPD was performed with an X-ray diffraction system (PANalytical, X'Pert PRO diffractometer) using the detector pixcel. The powders were exposed to Cu-K_α radiation source at 45kV and 40 mA. Diffractions patterns were obtained in 2θ at a range of 2-80° using 0.02°C step size and 10°/min scan speed. The measurement was done with the application of X'Pert Highscore.

In-vitro dissolution studies of the solid dispersions:

The *in-vitro* drug dissolution study of the solid dispersions were performed using an 8 station USP 23 dissolution testing apparatus, Type II (Electrolab, India, model TDT-08L). Sodium lauryl sulfate, 1% w/v solution in 0.1N HCl and 0.067 M Phosphate Buffer, pH 6.8 (± 0.1) were used as dissolution media. Solid dispersions equivalent to 20 mg of BOS was dispersed in 450 mL of dissolution media. The temperature was maintained at 37°C ± 0.5°C and the dispersion was stirred at 50 RPM. At predetermined time intervals 5 mL of samples were withdrawn, filtered through Nylon 0.45µm filter (Millipore Millex-HN) and analysed spectrophotometrically at 265 nm. At each time of withdrawal, 5 mL of fresh corresponding medium was replaced. The cumulative amount of drug release was calculated from the regression line obtained for standard samples in 0.1N HCl as well as 0.067 M Phosphate Buffer, pH 6.8 (± 0.1).

Statistical analysis:

The dissolution profile obtained for the solid dispersions were statistically analysed and compared using fit factors described by Moore and Falnner [14], adopted by the Food and Drug Administration guidance for dissolution testing. Briefly, fit factors are model independent methods that directly compare the difference between percent drug dissolved per unit time for a test and a reference product. The statistical analysis was carried out to evaluate the dissolution profile by the calculation of similarity and dissimilarity factor. The similarity factor (f_2) was defined by Food and Drug Administration (FDA) as the 'logarithmic' reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and references release profiles. Dissimilarity or, difference factor (f_1) describes the relative error between two dissolution profiles. It approximates the percent error between the curves.

RESULTS AND DISCUSSION

Results:

Solubility parameter calculation [Hansen solubility parameters (δ)]:

Compounds with similar values of δ are likely to be miscible. It was demonstrated that compounds with a $\Delta\delta < 7.0$ $(MPa)^{1/2}$ were likely to be miscible. When the $\Delta\delta > 10(MPa)^{1/2}$, the compounds were likely to be immiscible. The small difference between the calculated solubility parameters of the polymers and BOS indicated that BOS is likely to be miscible with Eudragit® L 100 55 (data not shown).

Solid dispersions of BOS by fusion technique:

The solid dispersion samples were prepared with the binary composition of BOS to the polymers in a ratio 1:1, 1:2 and 1:3 by fusion technique utilizing the utilizing Eudragit® L 100 55, Eudragit® EPO and Povidone K 30 as the carrier agent. This technique also yielded reasonably good dry powders. The recovery of powders from the process was more than 75%. The BOS content of the solid dispersions ranged from 90-100% of the anticipated amount and the moisture content for the solid dispersions lies between 1.40 to 2.20 (% w/w). The moisture content of BOS was observed to be 3.17%. The results revealed reasonable compressibility and flowability characteristics. The results are recorded in table 1.

Solid dispersions of BOS by solvent controlled coprecipitation technique:

The solid dispersion samples were prepared with the binary composition of BOS to the polymers in a ratio 1:1, 1:2 and 1:3 by solvent controlled coprecipitation technique utilizing same polymers as by the above technique as the carrier agent. This technique yielded reasonably good dry powders. The recovery of powders from the process was more than 60%. Higher polymer concentration even resulted about 90% recovery. The BOS content of the solid dispersions ranged from 90-100% of the anticipated amount and the moisture content lies between 1.90 and 3.02 (% w/w). The results revealed reasonable compressibility and flowability characteristics. The results are recorded in table 1.

Solid dispersions of BOS by nanoprecipitation technique:

The solid dispersion samples were prepared with the binary composition of BOS to the polymers in a ratio 1:1, 1:2 and 1:3 by nanoprecipitation technique utilizing the same polymers as by the above technique. This technique yielded reasonably good dry powders. The recovery of powders from the process was in between 50% to around 75%. The BOS content of the solid dispersions ranged from 90-100% of the anticipated amount and the moisture content for BOS and the solid dispersions was below 3.0 (% w/w). The results revealed reasonable compressibility and flowability characteristics. The results are recorded in table 1.

Characterization of solid dispersions:

The details of flow and compression characteristics of BOS and different solid dispersions samples are recorded in table 1. The solid dispersions showed comparable micromeritic, flow and compressible properties. The angle of repose for the drug powder BOS is obtained as 40°. For solid dispersions it ranged from 24° to 34°. The solid dispersions (in particular fusion technique samples) showed better compressibility indices than that of BOS which may be due to the hybrid denser particles of drug inside the polymer matrix. The particles of the solid dispersions prepared by all the above mentioned techniques have reasonable porous nature. However, the porosity of the solid dispersions prepared by solvent controlled coprecipitation technique and nano-precipitation technique was higher. The presence of moisture is a crucial characteristic for the solid dispersions as they could induce instability. The solid dispersion samples prepared by fusion technique have moisture content less than 2.2% w/v which may be due to the application of heat during the processing. The solid dispersions prepared from solvent controlled coprecipitation technique and nanoprecipitation technique possess higher amount of moisture (< 3.5%).

The size of the dispersions corresponding to the solid dispersions by nanoprecipitation technique are observed and recorded in table 2 and the average size ranged from 50 nm to 600 nm. However, the polydispersibility index was high. The increase in polymer concentration led to higher particle size in the preparations corresponding to all the three polymers.

X-ray Powder Diffractometry (XRPD):

The extent of crystallinity affects dissolution of drugs. Generally, amorphous or, metastable form will dissolve faster because of its higher internal energy and greater molecular motion compared to crystalline materials. Crystallinity was determined by comparing some representative peak heights in diffraction patterns of the solid dispersions with those of pure drug. The XRPD pattern of BOS, placebo and the solid dispersions by different techniques is presented in Figure 1. The presence of numerous distinct peaks in the diffractrogram of BOS reveal the crystalline nature of BOS with characteristic diffraction peaks appearing at 9.20, 18.54 and 18.67.

The solid dispersions prepared by solvent controlled coprecipitation technique suggest that the sample containing lower concentration of Eudragit® EPO (BCPE1) and Eudragit® L 100 55 (BCPL1) have shown the characteristic peaks of BOS in the diffractograms although the intensity is very low indicating partial crystalline nature. The peak intensities are significant in solid dispersions with Povidone K 30 at both the ratio 1:1 and 1:3. Solid dispersions with the other two polymers Eudragit® EPO and Eudragit® L 100 55, have shown amorphous solid dispersions in presence of higher concentration of polymers (BHME3 and BHML3).

The solid dispersions prepared by nano precipitation technique, have shown the presence of characteristic peak of BOS in the solid dispersion samples corresponding to all the three polymers. However, the intensity was lower in the case of preparations corresponding to Eudragit® L 100 55.

In solid dispersions prepared by fusion technique both the preparations with Eudragit® L 100 55 and Povidone K 30 yielded amorphous dispersions even at 1:1 ratio. At lower ratio of 1:1 Eudragit® EPO shows partially crystalline BOS. Thus, fusion technique generally yields an amorphous dispersion whereas, nanoprecipitation gives crystalline dispersion. Coprecipitation on the other hand gives amorphous dispersion when the polymer concentration is high. The nature of the drug in the solid dispersion also appears to depend on the nature of polymers as Povidone K 30 even in higher concentration yielded crystalline dispersions.

In-vitro dissolution studies of the solid dispersions:

The powder dissolution data reported in Figure 2 shows that the dissolution profile of BOS as such was the lowest of all, with no more than 10% dissolved within 2 hours in both the media. The presence of SLS in the dissolution media also could not improve the dissolution BOS. In comparison to this, the release of BOS was improved from different solid dispersions in the two dissolution media.

Solid dispersions prepared with Eudragit® L 100 55 have shown higher dissolution in pH 6.8 phosphate buffer irrespective of the technique used. For the solid dispersions prepared by all the three techniques, it reached near complete dissolution in 90 minutes. The dissolution appears to be higher and faster at higher polymer concentration. For formulation prepared with Eudragit® EPO, the extent of dissolution was much lower in all the three techniques. However, amongst the three techniques, nanoprecipitation method produced dissolution of upto 30% in 60 min at higher ratio of polymer. The solid dispersions prepared using solvent controlled coprecipitation yielded lowest dissolution level of about 19% in 60 min. The lower rate of dissolution with preparations corresponding to Eudragit® EPO is expected at pH 6.8 since the polymer dissolves in acidic media. Thus, it should resist the drug release at pH 6.8.

In contrast to this, neutral polymer Povidone K 30 has also shown lower rate of dissolution. The highest percent dissolution was about 39%. Further, with both the above polymers, the dissolution dropped significantly after reaching a peak indicating drug precipitation. On the contrary, preparations made with Eudragit® L 100 55 did not show such a drop.

In the acidic medium 0.1 N HCl containing SLS, drug as such showed similar extent of low dissolution. The dissolution reached about 11% in 120 min. In this medium, preparations made with Eudragit® EPO showed maximum dissolution of about 32% in 60 minutes irrespective of the method of preparation used. Thereafter, the dissolution profile shows significant drop up to 120 min indicating reprecipitation of the drug.

In the case of preparations made from neutral polymer Povidone K 30, similar trend is observed in the solid dispersions made by all the three techniques. The highest dissolution value observed is 36% with solvent controlled coprecipitation technique, it was 29% by fusion method and about 54% in the preparation with nanoprecipitation technique. However, reprecipitation of the drug was evident in all the samples prepared with all the three techniques.

For preparation made with Eudragit® L 100 55, the extent of dissolution was found to be the highest in the dispersions made with all the three techniques. The drug polymer ratio had a significant influence on dissolution. Further, no drop in the dissolution could be observed up to 120 min any of the samples except for the samples prepared by nanoprecipitation method at 1:1 drug polymer ratio (BNPL1).

High drug dissolution with Eudragit® L 100 55 is surprising in the acidic media since Eudragit® L 100 55 dissolves only at higher pH and is expected to hold the drug and prevent its release at low pH when the polymer does not dissolve.

Higher dissolution of the drug in acid media is attributable to the porosity of the solid dispersion and the presence of SLS in the medium. Coupled to this, the solubilization effect of Eudragit® L 100 55 towards the drug BOS because of its acidic functional group might aid in holding the drug in solid dispersion and then release it under acidic conditions in a controlled manner. Irrespective of the media used, a rank order relation between BOS products and their dissolution was evident.

BOS<SDs of BOS (Eudragit® EPO) <SDs of BOS (Povidone K 30) < SDs of BOS (Eudragit® L 100 55)

Statistical analysis:

Analysis of the similarity and difference factors (table 3) suggested that f_1 values of test samples is not close to zero and nor it lies between 0-15. This states that there is a substantial difference between the dissolution profiles of the test samples with that of controls. Considering arbitrarily, as $f_1 \geq 10$ or $f_2 \leq 50$, the curve was considered to be substantially different from that of the controls. Therefore, the solid dispersions prepared with Eudragit® L 100 55 (test samples) with different techniques have an edge and significantly different and improved dissolution profile than that of the controls in both the dissolution media irrespective of the pH of the media.

Table No. 1: Physico-Chemical characterization and micromeritics properties of solid dispersions of bosentan

S. No.	Techniques	Polymer	Ratio	Code	MC (%)	Assay (%)	BD (g/mL)	TD (g/mL)	CI (%)	HR	P (%)	AR (°)
1	NA	NA	NA	BOS	3.17	99.80	0.21	0.26	19.08	1.24	37.36	40.00
2	Fusion	Eudragit L 100 55 (Anionic)	R 1:1	BHML1	1.50	96.48	0.36	0.45	21.43	1.27	54.91	25.00
3			R 1:2	BHML2	1.70	95.27	0.42	0.50	16.67	1.20	50.89	25.00
4			R 1:3	BHML3	1.85	98.91	0.42	0.50	16.67	1.20	49.16	24.00
5		Eudragit EPO (Cationic)	R 1:1	BHME1	1.40	96.48	0.33	0.42	20.00	1.25	59.35	25.00
6			R 1:2	BHME2	1.45	96.61	0.36	0.42	14.56	1.17	58.11	25.00
7			R 1:3	BHME3	2.00	97.58	0.38	0.50	23.08	1.30	53.92	25.00
8		Povidone K 30 (Nonionic)	R 1:1	BHMP1	1.60	90.18	0.36	0.42	14.29	1.17	54.86	26.00
9			R 1:2	BHMP2	1.80	90.30	0.37	0.45	19.26	1.24	54.45	25.00
10			R 1:3	BHMP3	2.21	97.70	0.42	0.50	16.67	1.20	49.16	27.00
11	Solvent controlled coprecipitation	Eudragit L 100 55 (Anionic)	R 1:1	BCPL1	2.61	96.73	0.25	0.31	20.00	1.25	68.63	30.00
12			R 1:2	BCPL2	2.29	95.27	0.25	0.29	15.00	1.18	70.40	32.00
13			R 1:3	BCPL3	2.28	96.85	0.24	0.30	20.39	1.26	70.50	32.00
14		Eudragit EPO (Cationic)	R 1:1	BCPE1	2.35	93.45	0.24	0.31	23.81	1.31	70.99	33.00
15			R 1:2	BCPE2	1.90	93.82	0.24	0.29	19.05	1.24	71.85	33.00
16			R 1:3	BCPE3	2.72	97.33	0.24	0.29	19.05	1.24	71.42	34.00
17		Povidone K 30 (Nonionic)	R 1:1	BCPP1	2.78	92.00	0.23	0.31	27.27	1.38	71.45	30.00
18			R 1:2	BCPP2	2.87	93.58	0.23	0.31	27.27	1.38	71.89	30.00
19			R 1:3	BCPP3	3.02	97.82	0.25	0.31	20.00	1.25	69.52	30.00
20	Nanoprecipitation	Eudragit L 100 55 (Anionic)	R 1:1	BNPL1	2.50	93.45	0.25	0.31	19.00	1.23	68.44	32.00
21			R 1:2	BNPL2	2.80	94.79	0.28	0.31	10.00	1.11	67.26	32.00
22			R 1:3	BNPL3	2.85	98.30	0.28	0.31	10.56	1.12	66.11	32.00
23		Eudragit EPO (Cationic)	R 1:1	BNPE1	2.70	93.70	0.24	0.30	20.48	1.26	70.96	33.00
24			R 1:2	BNPE2	2.75	96.61	0.27	0.30	10.81	1.12	68.20	32.00
25			R 1:3	BNPE3	2.71	97.58	0.27	0.31	11.41	1.13	67.45	31.00
26		Povidone K 30 (Nonionic)	R 1:1	BNPP1	2.60	95.88	0.25	0.31	20.00	1.25	68.40	32.00
27			R 1:2	BNPP2	2.84	95.27	0.28	0.31	11.11	1.13	65.52	33.00
28			R 1:3	BNPP3	2.90	96.00	0.28	0.32	12.50	1.14	66.11	32.00

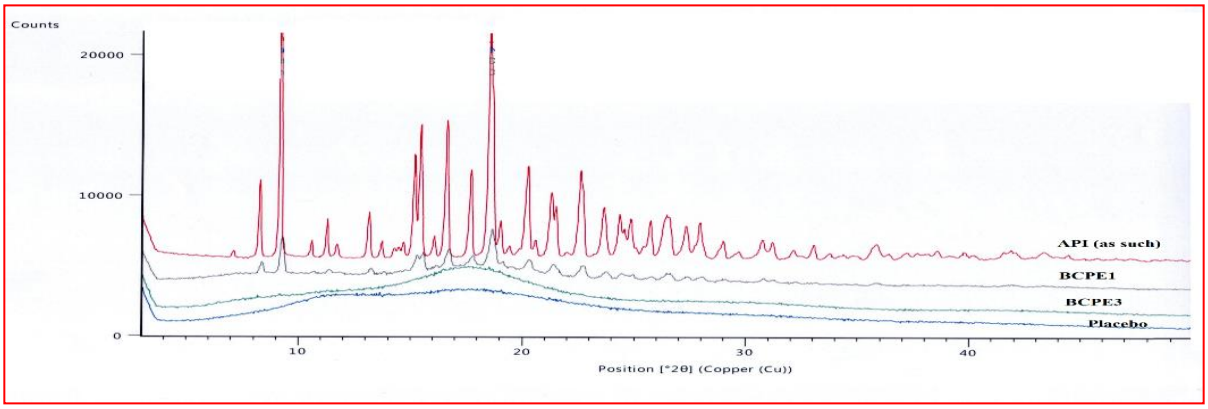
NA: Not applicable; MC: Moisture content, BD: Bulk density; TD: Tapped density, CI: Carr's compressibility index, HR: Hausner's ratio, AR: Angle of repose, P: Porosity

Table No. 2: Characteristics of different preparations of from bosentan in Milli Q water in nanoprecipitation technique

S. No.	Polymers	Ratio	Sample Code	Average size (nm)	Polydispersity index
1	Eudragit® L 100 55	R 1:1	BNPL1	53.77	0.441
		R 1:2	BNPL2	511.8	0.338
		R 1:3	BNPL3	558.6	0.52
2	Eudragit® EPO	R 1:1	BNPE1	182.5	0.186
		R 1:2	BNPE2	199.4	0.193
		R 1:3	BNPE3	228.4	0.278
3	Povidone K 30	R 1:1	BNPP1	183.1	0.524
		R 1:2	BNPP2	254.8	0.794
		R 1:3	BNPP3	479.2	0.198

Table No. 3: Statistical treatment to the dissolution profile of respective solid dispersions of BOS with Eudragit® L 100 55 prepared by different techniques

	f_1			f_2		
Dissolution medium	BOS	BCPE3	BCPP3	BOS	BCPE3	BCPP3
0.1 N HCl	88.18	58.02	42.47	15.52	20.12	24.87
pH 6.8 phosphate buffer	94.94	84.57	71.57	4.31	6.70	10.25
	BOS	BHME3	BHMP3	BOS	BHME3	BHMP3
0.1 N HCl	91.69	69.01	70.91	7.85	12.39	13.14
pH 6.8 phosphate buffer	94.41	81.89	73.52	6.07	9.21	11.55
	BOS	BNPE3	BNPP3	BOS	BNPE3	BNPP3
0.1 N HCl	92.04	73.96	54.56	7.85	11.19	14.12
pH 6.8 phosphate buffer	94.52	73.77	71.13	6.08	10.82	12.63



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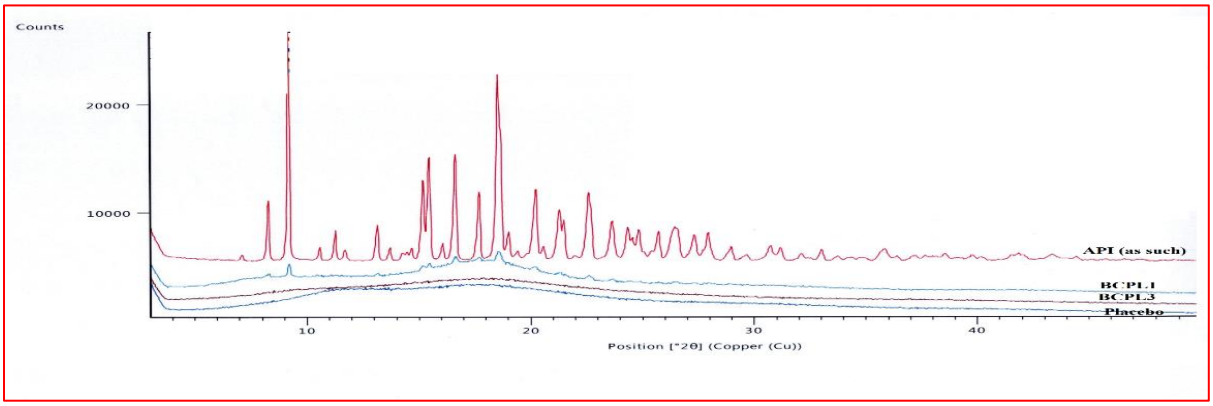

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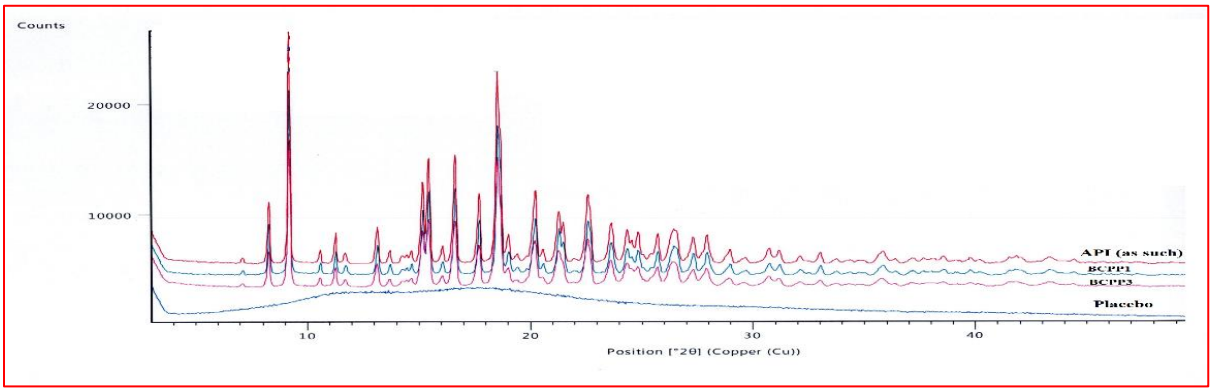

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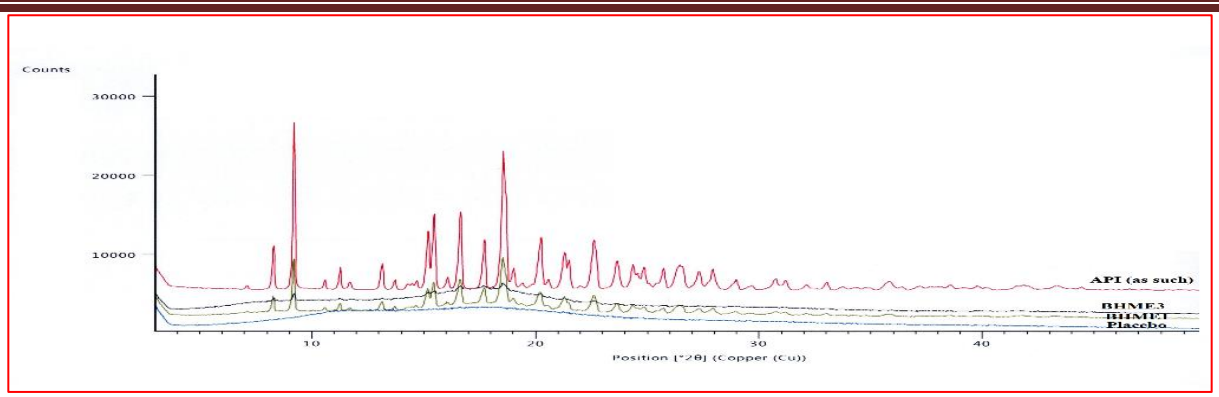

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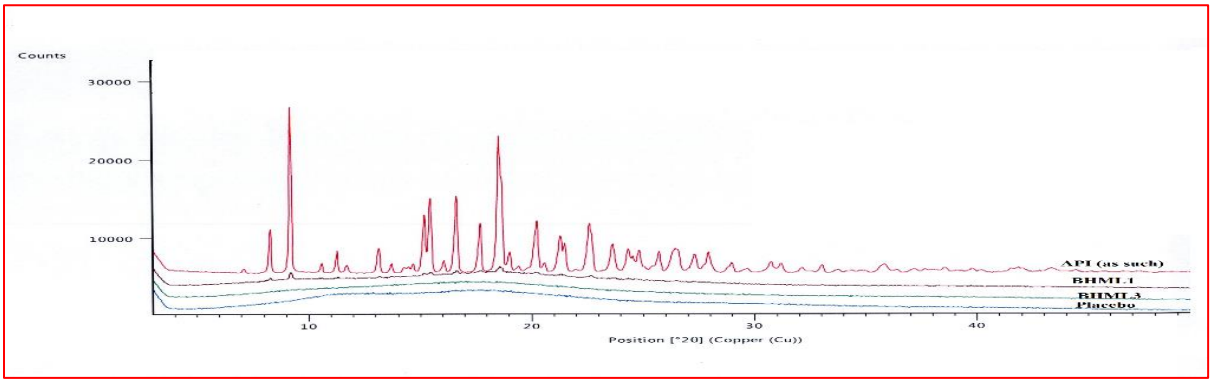

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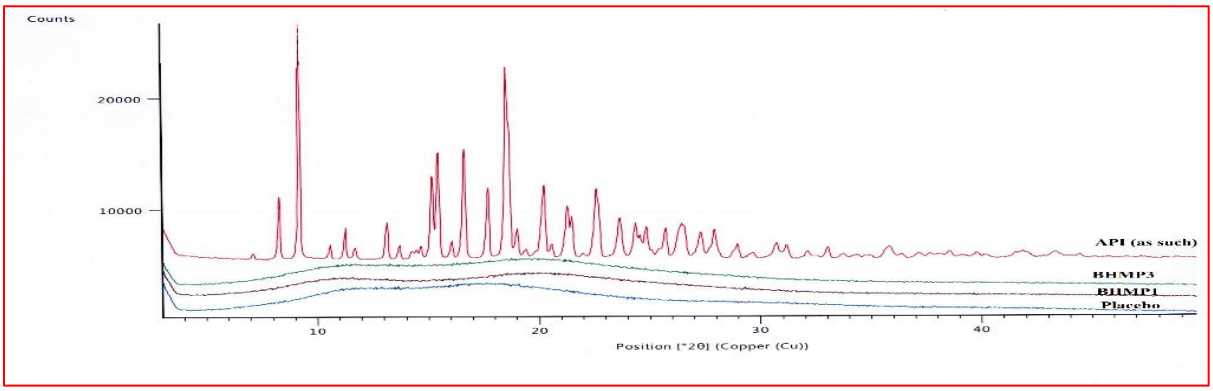

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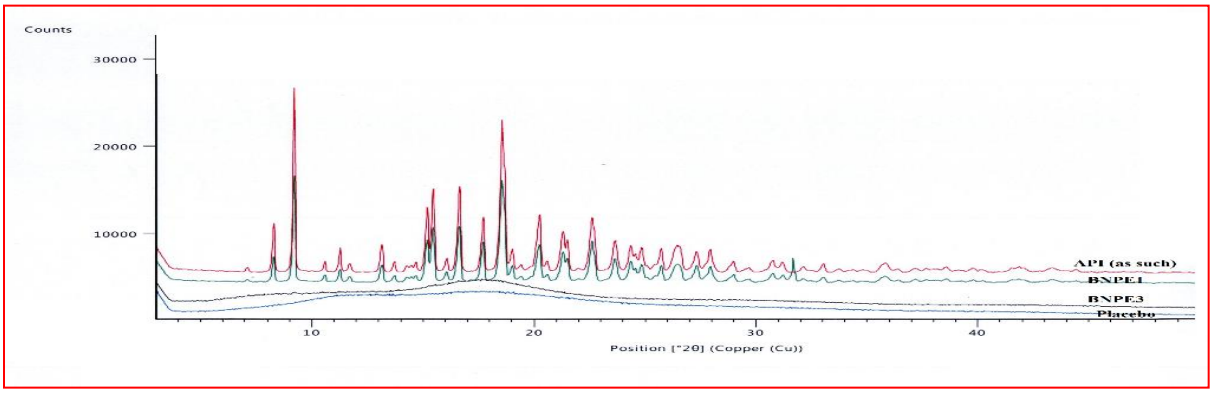

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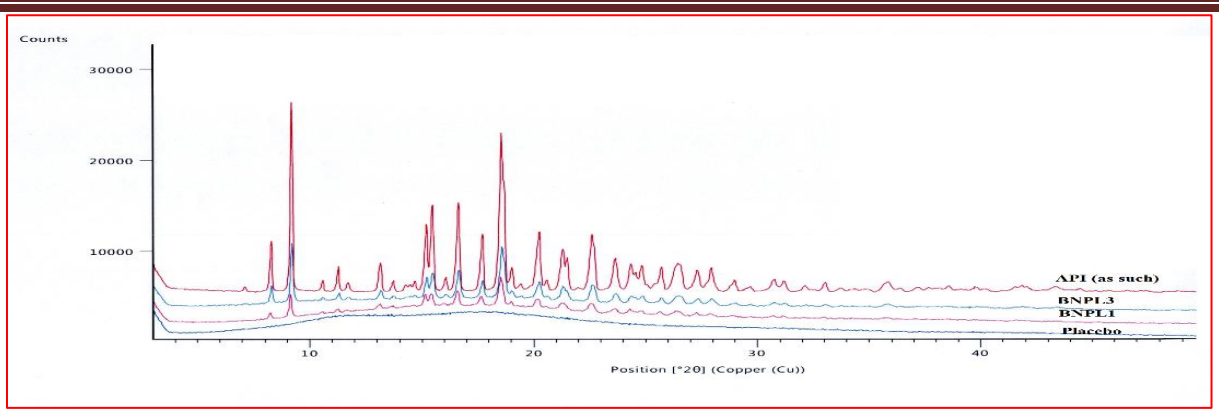

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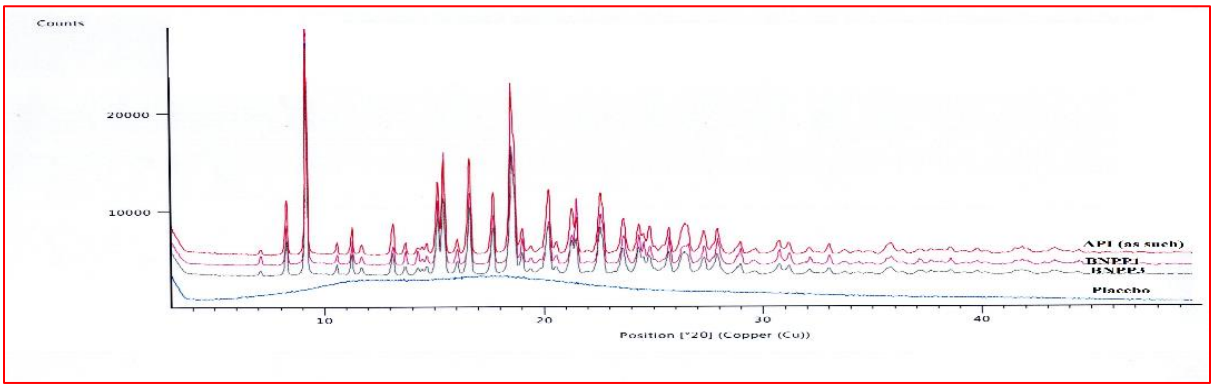

I

Fig. 1: X-ray powder diffraction pattern summarizing the comparative diffractogram of BOS, placebo and different solid dispersions prepared by solvent controlled coprecipitation technique from (A) Eudragit® EPO (BCPE1 and BCPE3), (B) Eudragit® L 100 55 (BCPL1and BCPL3), (C) Povidone K 30 (BCPP1and BCPP3); by fusion technique from (D) Eudragit® EPO (BHME1and BHME3), (E) Eudragit® L 100 55 (BHML1and BHML3), (F) Povidone K 30 (BHMP1and BHMP3); by nanoprecipitation technique from (G) Eudragit® EPO (BNPE1and BNPE3), (H) Eudragit® L 100 55 (BNPL1and BNPL3) and (I) Povidone K 30 (BNPP1and BNPP3).

Discussion:

It is evident that the dissolution rate of the solid dispersions of BOS prepared with Eudragit® L 100 55 are higher than that of pure drug and the solid dispersions prepared with the other polymers i.e. Eudragit® EPO and Povidone K 30. The possible elucidations of the increased dissolution rate of solid dispersions have been proposed by Craig and Ford [15, 16], which encompasses reduction of drug crystallite size, a solubilization effect of the carrier, absence of aggregation of drug crystallites, improved wettability and dispersibility of the drug, dissolution of the drug in the hydrophilic carrier, conversion of the drug to the amorphous state and finally the combination of the above mentioned mechanisms. We observed hike in the drug release from the solid dispersions in the dissolution media which may be attributed to any of the above mechanisms or, combination thereof. The ultimate success of a solid dispersion is determined by its performance in dissolution after oral administration. The general strategy behind almost all solubilization technologies is the so called "spring-and-parachute" concept [17]. For a solid dispersion, this means that the drug should first dissolve along with the soluble polymer matrix to create a supersaturated solution ("the spring") after which supersaturation is maintained long enough for drug absorption ("the parachute") to take place.

Generally, solid dispersions generate a supersaturated drug solution when exposed to the aqueous environment of the gastrointestinal tract. Drugs in this state have a tendency to precipitate rapidly before being absorbed resulting in reduced bioavailability. A variety of polymer excipients have been evaluated for their ability to prolong the supersaturation and inhibit drug precipitation [18]. The researchers have reported different polymers like hydroxypropyl methylcellulose (HPMC) and hydroxypropylmethylcellulose acetate succinate (HPMCAS) and vinyl polymers such as poly (vinylpyrrolidone) (PVP) and poly(vinylpyrrolidone-co-vinyl acetate) (PVPVA) which are employed not only as carriers for solid dispersions but are also meant for inhibiting drug precipitation. In the present study, we have employed polymers with different ionic nature like Eudragit® L 100 55 (anionic), Eudragit® EPO (cationic) and Povidone K 30 (non-ionic) to evaluate the effect of the polymers in maintaining a supersaturated drug concentration in the dissolution medium.

It was observed that the solid dispersions of BOS with Eudragit® L 100 55 show better release profile without any significant drop in the drug release. The increase in the dissolution may be attributed to the interaction of drug with the polymer or, changing the properties of the medium or both [19, 20] or, suppressing the nucleation process [21] or, adsorbing on the surface of crystals to block the access of solute molecules ("the poisoning effect") thus preventing or retarding crystal growth [22, 23]. It is evident from the in silico studies that Eudragit® L 100 55 interacts with BOS. The interaction between BOS and Eudragit® L 100 55 may be due to the hydrogen bond formation and/or hydrophobic interactions.

The hydrogen-bond acceptors in BOS may be interacting with Eudragit® L 100 55 alluding about the effectiveness of Eudragit® L 100 55 in inhibiting nucleation and recrystallization [24-26] in a concentration dependent manner. The process of delaying of nucleation and inhibition of recrystallization may be not only due to the increase in the nucleation activation energy but also reduce crystal growth [27-29]. Many researchers have discussed different characteristic features of drug and polymer in the hydrogen bonding interaction. The lipophilicity of the polymers, rigidity of the polymers, adsorption onto the crystal surface resulting in steric hindrance and few other factors have been discussed [30-37]. The interaction *via* hydrogen bonding between the carboxyl group of the anionic methacrylate co-polymer and -NH group of BOS was the basis for the interaction strength. This interaction has been well depicted by the solubility parameter showing that $\Delta\delta < 7.0$ $(MPa)^{1/2}$ implying of better miscibility of the drug in the polymer. However, it should also be noted that the solubility of the drug in the polymer is not enough to prevent the recrystallization and improvement in the drug release.

Dissolution profiles of solid dispersions with Eudragit®L 100 55 showed an increase in the dissolution rate of BOS with respect to the drug by itself which could be due to the acidic nature of the polymer. It is also clear that increasing the weight fraction of BOS in the solid dispersions did not affect noticeably the dissolution rate of the solid dispersions. The dissolution mechanism of solid dispersion with Eudragit® L 100 55 might be predominantly diffusion-controlled, and presumably the high viscosity of this carrier in stagnate layer is the main factor to control the dissolution rate. The supersaturation of bosentan was effectively prolonged in the presence of Eudragit® L 100 55.

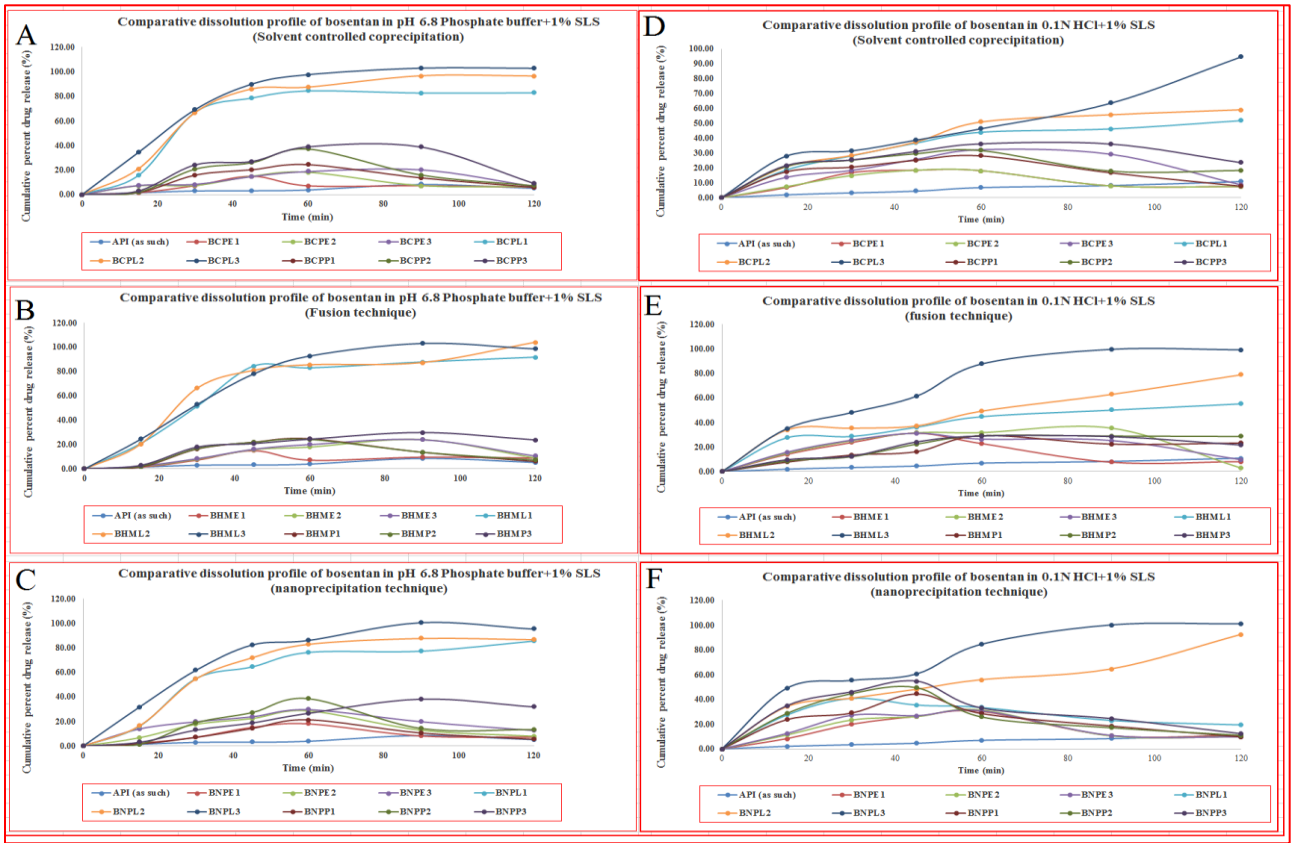

Fig. 2: Cumulative release of BOS from solid dispersions (A) solid dispersions by solvent controlled coprecipitation technology, (B) solid dispersions by fusion technique (C) solid dispersions by nanoprecipitation technique in 0.067 M Phosphate Buffer, pH 6.8 + 1% w/v SLS; (D) solid dispersions by solvent controlled coprecipitation technology, (E) solid dispersions by fusion technique (F) solid dispersions by nanoprecipitation technique in 0.1 N HCl + 1% w/v SLS: Each value represents the mean ± SD, (n=3).

In general, drug release from the solid dispersions occur in different possible ways like a) dissolution of drug and polymer in the solid dispersion in a rapid manner then subsequently undergo absorption and precipitation in the presence of polymer and endogenous compounds such as bile acids, phospholipids and mucin as described for low drug loaded solid dispersions and b) it is also explained that during this dissolution process, various structures may form including free drug (the major species, if not the only species, being absorbed, so its concentration is what matters for absorption), drugs in bile salt/phospholipid micelles, amorphous drug nanoprecipitates with polymers, and possibly drug nanocrystals stabilized with polymers, all of which are in dynamic exchange with each other [38].

We have attempted to achieve pH-independent release of BOS from hydrophilic matrices by incorporation of polymers of different ionic characteristics to compare the release behaviour. The solid dispersions prepared with Eudragit® L 100 55 (anionic) are presumed to lower the release in the acidic environment by forming an insoluble mass which may act as barrier to drug diffusion and enhance release in a high pH environment. However, we observed that in spite of having low permeability of Eudragit® L 100 55 to 0.1N HCl significant improved release behaviour was observed for the solid dispersions with Eudragit® L 100 55 than the solid dispersions prepared from other polymers. BOS molecules could have been solubilized due to the acidity of the polymers and got released completely. Further, porosity of solid dispersion and presence of SLS could have aided the drug release under different conditions. In the case of nanoprecipitation, the drug is in crystalline form but the release is high. It is known that nanosize affects the solubility and the dissolution. Thus, this form also appears to aid in creation of supersaturated state that is subsequently stabilized by the polymer.

We have attempted three novel techniques like solvent controlled coprecipitation, fusion and nanoprecipitation for preparing the solid dispersions of BOS. In spite of having differences in the preparation procedure and other physico chemical properties, it was observed that judicious choice of polymer and technique are prerequisite of preparing solid dispersion formulation development of any drug. Drug-polymer interaction through hydrogen bonding or, any other electrostatic interaction play a get role in achieving drug-polymer miscibility and maintenance of super saturation in the gastric milieu for a period.

It is also evident that the presence of crystalline peaks in the diffractograms of different solid dispersions is not affecting the dissolution. The solid dispersions prepared with different concentrations of Eudragit® L 100 55 by nanoprecipitation technique have shown better release profile than the solid dispersions prepared from Eudragit® EPO with the same technique in spite of the absence of the peaks in the diffractogram of BNPE3. Although the solid dispersions prepared by the same technique with Eudragit® L 100 55 have the peaks in the diffractogram, the release profile was significantly better than the other solid dispersions.

Porosity provides pathways for the penetration of fluid into the powder through capillary action and resulted in rupture of inter-particulate bonds causing the powder to break and the change in the

morphological form contributed to the dissolution velocity enhancement. The solid dispersions prepared from the solvent controlled coprecipitation technology and nanoprecipitation technique have shown a porosity of 65 to 70%. However, the solid dispersions obtained from fusion technique exhibited lower porosity of 49 to 55% which is however higher than BOS itself (37%) and is attributed to the molten stringent polymer layer on the particles.

The release behaviour indicate solubilization is related to the ionic nature of the polymer. The polymer-specific properties of Eudragit® L 100 55 prolonged supersaturation by increasing media viscosity and interaction with BOS are attributing for the inhibiting behaviour against crystallization.

CONCLUSION

As an increasing proportion of drugs undergoing development are poorly water-soluble, solubilization technologies have become an essential feature in bringing them successfully to market. The solid dispersion is one such technology which in recent years has led to the approval of a large number of products, suggesting it is now the preferred technology for drug solubilization. These results emphasize that mechanisms of supersaturation could differ significantly depending on the specific drug-polymer combination.

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