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ENHANCEMENT OF DISSOLUTION OF POORLY SOLUBLE BOSENTAN BY DIFFERENT NOVEL TECHNIQUES OF SOLID DISPERSION

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ABSTRACT

Bosentan presents challenges with regard to its low and variable oral bioavailability in its formulation development. These challenges are due to its poor aqueous solubility and poor dissolution in the gastric fluid. In the present investigation, different techniques of solid dispersions have been used utilizing various polymers at different ratios to improve solubility and dissolution rate. Solid dispersions of bosentan were prepared by using novel techniques like solvent controlled coprecipitation, fusion, nanoprecipitation and spray drying. Solid dispersions of weakly basic bosentan were prepared utilizing polymers with different ionic characteristics like Eudragit® EPO (cationic), Eudragit® L 100 55 (anionic), HPMCP HP 55 (anionic), HPMC AS (anionic) and Povidone K 30 (non-ionic) at three different ratios of 1:1, 1:2 and 1:3. Dissolution study in buffers corresponding to different physiologically relevant pH was performed to understand the effectiveness of the techniques 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 solid dispersion systems. It was observed that irrespective of the pH of the dissolution media, solid dispersions prepared with anionic polymers especially, HPMCP HP 55 have shown better release than the solid dispersions with 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. Solid dispersion technology in combination with supersaturable systems concept appear to hold promise for improving dissolution and bioavailability of poorly soluble drugs. The judicious selection of polymers at optimized ratio which can inhibit or, delay the crystallization of the drug in a supersaturated state becomes the key factor for an effective formulation and therapeutic outcome. The present work is an attempt in this direction.

INTRODUCTION:

The development of effective formulation approaches to facilitate oral absorption of poorly water-soluble drugs is a considerable challenge as water solubility has always been a key obstacle in pharmaceutical formulations. Formulation development such poorly water-soluble compounds continues to be a great challenge due to their intrinsically low solubility and poor oral absorption [1]. In drug discovery, there is emergence of different advanced techniques like high-throughput screening and different combinatorial screening programs to tackle unprecedented drug targets. These have resulted in the advent of different poorly soluble molecules with bioavailability challenges. It is estimated that approximately 40% of currently marketed drugs and 75% of drugs under development which are poorly soluble in water are being identified through these screening programs. It is also speculated that at least 50% of the new chemical entities (NCEs) under development will have very poor solubility and hence low bioavailability [2, 3, 4].The formulation development of such poorly soluble molecules is a challenging task for researchers to increase their solubility and bioavailability as well as reformulate generic drugs. Solubility of the active pharmaceutical ingredient below 1μg/mL, is a persistent problem since many years and worth attempting new development technologies to improve the solubility and bioavailability [5, 6]. The Biopharmaceutical Classification System (BCS) groups poorly soluble compounds as Class II and IV drugs, compounds which feature poor solubility, high permeability and poor solubility poor permeability respectively. According to this system, drugs belonging to Class II having good permeability property exhibit limited bioavailability due to their poor solubility. There are a number of formulation strategies reported which can be approached to improve the bioavailability of BCS Class II drugs either by increasing the dissolution rate or by maintaining the drug in solution state in the gastrointestinal tract. There are a number of formulation strategies those present the platform to improve the bioavailability of Class II drugs whereas, the bioavailability of Class IV drugs may be improved by different formulations, but they are likely to be compromised by their membrane permeability. This issue is relevant for BCS class II and class IV drugs. Interestingly, the paradigm of this long existing problem is now shifting to a point where some of the NCE have both poor aqueous and organic solubilities [7]. The need to improve the solubility and bioavailability of poorly-soluble compounds has been identified as the driving force towards the advent of different formulation development strategies. The routine solubility enhancing techniques like co-solvent addition, pH modification, heat application, particle size reduction do not always resolve the solubility issues and as a result of which researchers have also developed advanced formulation strategies to improve the solubility of poorly soluble drugs. These include complexation with cyclodextrins [8, 9], polymeric nanoarchitecture [10], self-emulsifying drug delivery system [11], emulsions and microemulsion, nano suspensions, micellar solubilization and solid dispersion [12]. In the improvement of oral bioavailability of poorly water-soluble drugs, different approaches have been designed which are intended to increase apparent equilibrium solubility in the gastrointestinal (GI) tract or, to increase the rate of dissolution. However, it has been realized by different researchers that maintenance of a temporary state of supersaturation may be sufficient to promote absorption especially for highly permeable

molecules. In this approach, supersaturated formulations resulting exceeding drug concentration beyond equilibrium solubility in the GI fluids have been designed. This exceeding drug concentration is supposed to improve the absorption. However, thermodynamic instability of drug at high concentrations results in the rapid precipitation *in-vivo* before being absorbed, resulting in compromised bioavailability. Therefore, in the design of the formulations, researchers consider the utilization of different precipitation inhibitors to maintain the supersaturation, improve the stability aspects and to prevent precipitation of the drug. Depending upon the interaction capabilities of these inhibitors with the drug, they maintain drugs in the supersaturated state and retard drug precipitation for a period of time, allowing sufficient absorption for increasing oral bioavailability. These agents are important component of solid dispersions and thus can be utilized in the stabilization of high energy systems. The precipitation inhibitors used in supersaturable formulations for poorly water-soluble compounds include polymers, surfactants and cyclodextrins. A number of different formulating approaches have been used in order to create supersaturation of drug in the GI tract and thereby increase absorption of low solubility compounds. The amorphous solid dispersion is normally stabilized by making a molecular dispersion between carriers (typically a polymer). This result in the locking of the drug in an amorphous state with an apparent higher solubility than the crystalline solubility [13-22]. 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 many marketed product based upon this technology. The main reason behind this are the stability and scale up problems associated with this technology, as reported by several authors [23]. 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, small crystalline or, partially crystalline form. 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 dual endothelin receptor antagonist indicated mainly in the management of pulmonary artery hypertension. 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. 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 [24, 25, 26]. Typically, the solubility behaviour of weakly ionisable compounds is strongly dependent on pH of the gastric milieu. The pH-dependent solubility characteristics of weakly basic drugs like BOS, possibly result in low and incomplete release of these drugs from different conventional formulation approaches due to the exposure of these dosage forms to high pH milieu for the majority of their gastrointestinal transit time. However, the development of pH independent release systems for delivery of such drugs not only ensures high release

throughout physiological pH, but also lowers intra- and interpatient variability in bioavailability [27, 28, 29]. A number of studies have been reported describing different formulation strategies to improve the solubility and dissolution rate of BOS. Lipid and surfactant based solid dispersions of BOS have been formulated to improve its solubility and dissolution rate by Panda et al [30]. Solubility improvement of BOS by complexation technology utilizing cyclodextrins has been studied by Pore et al [31]. As an introductory part of our research work, we have studied the dissolution improvement aspects of BOS by solid dispersion techniques by Mohanty *et al*. In continuation, the similar work has been taken forward and extended in this present investigation to include additional polymers and techniques. Hence, some part has been abstracted in the present investigation from the said introductory work [32]. The objectives of the present work were focused to improve the solubility of BOS by utilizing novel techniques of solid dispersions like solvent controlled coprecipitation, fusion, nanoprecipitation and spray drying. It is an attempt to prepare solid dispersions of bosentan with an objective to improve its dissolution. Rapid onset of 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. Hypromellose Phthalate (HPMCP HP55) and Hypromellose Acetate Succinate (HPMC AS MF) were supplied by Shin Etsu. 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 can be used as a powerful tool to determine the drug-polymer interactions through estimation of the strength of the interactions. It aims to estimate the solubility for binary combinations of BOS with commonly used polymers. Solubility parameters using van Krevelen methods, of both drugs as well as the polymers were calculated in order to determine the theoretical drug/polymer miscibility [33].

Preparation of solid dispersions of BOS

The different techniques used for the preparation of the solid dispersions of BOS are solvent controlled coprecipitation, fusion, nanoprecipitation and spray drying techniques. In all the techniques, solid dispersions were prepared using polymers with different ionic characteristics like Eudragit® EPO (cationic), Eudragit® L 100 55 (anionic), HPMCP HP 55 (anionic), HPMC AS (anionic), and Povidone K 30 (non-ionic) at three different ratios of 1:1, 1:2 and 1:3.

Solvent controlled coprecipitation technique

In this technique, BOS and the respective polymer were dissolved in N, N-Dimethyl acetamide (DMA). The solution was introduced at ambient temperature into the corresponding antisolvent kept under stirring at 2500 to 3000 rpm under a laboratory stirrer by spraying through a spray nozzle of diameter 1mmwith 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 preparations containing Eudragit® L 100 55, HPMCP HP 55 and HPMC AS MF, 0.067 M Phosphate Buffer(pH 6.8) for Eudragit® EPO containing preparation and water for Povidone K 30 containing preparation.

Fusion technique

In this technique, 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 to prevent the ingress of moisture**.** The resulting dried solid dispersion samples were characterized and analysed.

Nanoprecipitation technique

In this technique, the drug solution was prepared by dissolving BOS in ethanol (99%). The polymer solution were prepared basing upon their ionization behaviour. Anionic polymers like Eudragit® L 100 55, HPMCP HP 55 and HPMC AS MF were 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^{o}C with an angle of detection of 90^{o}. The mean size was directly obtained from the instrument. The drug polymer complex in the colloidal dispersions were further precipitated by addition of the corresponding antisolvent. The antisolvent used was 0.01 N HCl for preparations containing Eudragit® L 100 55, HPMCP HP 55 and HPMC AS MF, 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.

Spray drying technique

In this technique, BOS and polymers were dissolved in the suitable solvent (s) to prepare clear solution. The respective polymers were dissolved as per their ratio (w/w) of drug to the polymers in either single or, binary solvent system depending upon the solubility of BOS and polymers (total weight of the sprayed solution was 100 gm). Ethanol was taken as primary solvent for preparations made from BOS with polymers like Eudragit L 100 55, Eudragit EPO and Povidone K 30 whereas, preparations with HPMCP HP 55 were prepared by using ethanol: acetone at a ratio 50:50 ratio (w/w) and acetone: dichloromethane at a ratio 50:50 ratio (w/w) for the preparations with HPMC AS MF as the solvent system. Spray dried products were prepared using the spray dryer (Labultima, LU 222 Advanced). Nitrogen flow rate, sample concentration, and pump speed were each set. Other process parameters were fixed (inlet temperature: 70°C to 80°C; nozzle tip: 0.5 mm). All spray dried products were further suitably dried under vacuum.

Characterization of the solid dispersions

The solid dispersions were evaluated for different micromeritics properties like 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 analysed 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^o using 0.02^{o}C step size and 10°/min scan speed. The measurement was done with the application of X'PertHighscore.

***In-vitro* dissolution studies of 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 265nm. 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

Statistical evaluation of the dissolution profile obtained for the solid dispersions was done and compared using fit factors described by Moore and Flanner [34], adopted by the Food and Drug Administration guidance for dissolution testing. Theoretically, 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 anionic polymers (Eudragit® L 100 55, HPMCP HP 55 and HPMC AS MF) and BOS indicated that BOS is likely to be miscible with the anionic polymers.

Solid dispersions 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 Eudragit® EPO, Eudragit® L 100 55, Povidone K 30, HPMCP HP 55 and HPMC AS MF as the carrier agents. This technique yielded reasonably good dry powders. The recovery of powders from the process was more than 45%. The samples corresponding to higher polymer concentration even resulted above 70% recovery. This lower yield for few samples is attributed to the lower batch size with some loss during process. However, this loss can be minimized by improving the batch size. The BOS content of the solid dispersions ranged from 90-100% of the anticipated amount and the moisture content lies below 3.5 (% w/w). The results revealed reasonable compressibility and flowability characteristics. The results are recorded in table 1.

Solid dispersions by fusion technique

The solid dispersion samples were prepared with the binary composition of BOS to the respective polymers in a ratio 1:1, 1:2 and 1:3 by fusion technique utilizing the same polymers as by the above technique as the carrier agents. 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 below 2.5 (% w/w). The results revealed reasonable compressibility and flowability characteristics. The results are recorded in table 1.

Solid dispersions by nanoprecipitation technique

The solid dispersion samples were prepared with the binary composition of BOS to the polymers in 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 77%. This lower yield for few samples is attributed to the lower batch size with some loss during process. However, this loss can be minimized by improving the batch size. 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.

Solid dispersions by spray drying 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 spray drying 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 55% to around 92%. This lower yield for few samples is attributed to the lower batch size with some loss during process. However, this loss can be minimized by improving the batch size. The BOS content of the solid dispersions ranged from 90-100% of the anticipated amount and the moisture content for 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°. However, the angle of repose obtained for different solid dispersions was ranging from 24° to 46°. 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 due to the heat application during the process. The particles of the solid dispersions prepared by all the above mentioned techniques have reasonable porous characteristics. However, the porosity of the solid dispersions prepared by solvent controlled coprecipitation technique, nanoprecipitation and spray drying technique was higher (more porous by spray drying technique) than that of solid dispersions prepared by fusion technique. 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 2.21%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, however it lies below 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 observed to be high. The increase in polymer concentration led to higher particle size in the preparations corresponding to all the five 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 diffractogram 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 irrespective of the concentration of all the five polymers; the characteristic peaks of BOS in the diffractograms is prominent. In some of the preparations, the intensity of the peaks is very low indicating partial crystalline nature. On the other hand preparations made by fusion technique, resulted in amorphous nature. This observation was revealed for all the samples irrespective of the nature and concentration of the polymers. Where ever, peaks are obtained, those are highly diminished alluding about the substantial reduction of the crystallinity. This may be due to the reducing of crystal lattice energy with the application of heat. The samples prepared with nanoprecipitation technique has shown almost similar pattern crystallinity behaviour to that of the diffratograms of preparations from solvent controlled coprecipitation technique. The characteristic peaks of BOS are diminished in the preparations with BNPHP1 and BNPHP3. The higher ratio of the polymers have also shown presence of low intensity crystalline peaks.

***In-vitro* dissolution studies of the solid dispersions**

The powder dissolution data reported in Figure 2and 3 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 of BOS. In comparison to this, the release of BOS was improved from different solid dispersions in the two dissolution media. Solid dispersions prepared with anionic polymers have shown higher dissolution in both the media irrespective of the technique used. The dissolution appears to be higher and faster at higher polymer concentration. In both the media, solid dispersions prepared using solvent controlled coprecipitation have shown higher dissolution corresponding to the preparations with anionic polymers. In 0.1N HCl, the dissolution observed at the end of 2 hours was 95% for BCPL3, 100% for BCPHP3 and 96% for BCPAS3. However, the higher dissolution characteristic was not observed with BCPE3 and BCPP3. Similar, trend was also encountered with the dissolution of the preparations in 0.067 M Phosphate Buffer, pH 6.8 (± 0.1).The preparations from anionic polymers, prepared with fusion technique have shown complete dissolution in less than 2 hours but the preparations with Eudragit® EPO and Povidone K 30, have shown precipitation behaviour in the dissolution media as like the preparations from same polymers by solvent controlled coprecipitation technique. The lower rate of dissolution with preparations containing 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. Nonetheless, neutral polymer povidone K 30 has also shown lower rate of dissolution. The dissolution of samples corresponding to nanoprecipitation shows improved release

behaviour from the preparations with anionic polymers concluding of complete release within 120 min. 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 less than 44% in 60 minutes irrespective of the method of preparation used. Thereafter, the dissolution profile shows drop up to 120 min indicating reprecipitation of the drug. For the solid dispersions prepared with the anionic polymers by all the four techniques, it reached near complete dissolution in 90 minutes. For formulation prepared with Eudragit® EPO, the extent of dissolution was much lower in all the four techniques. However, amongst the four techniques, nanoprecipitation method produced dissolution of up to 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 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, HPMCP HP 55 and HPMC AS MF did not show such a drop. In the case of preparations made from neutral polymer Povidone K 30, similar trend is observed in the solid dispersions made by all the four techniques. The highest dissolution value observed is 36% with solvent controlled coprecipitation and spray drying 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 four 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 the three anionic polymers Eudragit® L 100 55, HPMCP HP 55 and HPMC AS MF is surprising in the acidic media since they 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 also 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, HPMCP HP 55 and HPMC AS MF towards BOS because of their 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)< SDs of BOS (HPMC AS MF) < SDs of BOS (HPMCP HP 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 control. 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 HPMCP HP 55 (test samples) with different techniques have an edge and significantly different and improved dissolution profile than that of the BOS (control) in both the dissolution media irrespective of the pH of the media.

However, the difference factor is minimal and even negligible when the dissolution profile of the test samples is compared with other controls.

DISCUSSION

The *in vitro* dissolution testing was performed for 120 minutes to ascertain the effect of formulations on immediate drug release enhancement. The different solid dispersions samples irrespective of the polymer increased the solubility and maximize the surface area of the drug that came in contact with the dissolution medium as the carrier dissolved. Theoretically, the common reasons attributing towards such increased dissolution rate are reduction of drug crystallite size, a solubilization effect of the carrier, absence of aggregation of drug crystallites, surface tension lowering effect of polymer, improved wettability, dispersibility of the drug, dissolution of the drug in the hydrophilic carrier, conversion of the drug to the amorphous state and combination thereof [29, 30]. It is evident that in both the media the dissolution rate of the solid dispersions of BOS prepared with the different anionic polymers Eudragit® L 100 55, HPMC AS MF and HPMCP HP 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. Here, the mechanism is also believed to be a microenvironment polymer effect facilitated by keeping the polymers and drug particles in close proximity during drug dissolution. In the case of pure drug, release was decreased than drug with the polymer. Whatever the improvement observed with solid dispersions corresponding to Eudragit® EPO and Povidone K 30 is attributed to wetting ability and convert crystalline to amorphous. But the improved drug polymer interaction, microenvironmental pH modulation and conversion of crystalline to amorphous drug particles are additional contributing factors for the significant improved dissolution behaviour observed for the preparations with anionic polymers. Basically, considering the fundamental aspects of any dissolution procedure, the two components i.e. drug and carrier (s) dissolve. This dissolution has been suggested to either be carrier-controlled (dominated by the properties of the carrier) or, drug-controlled (dissolution is driven by drug properties such as particle size and physical form). Whatever, may be the release mechanism, a concentrated polymer layer will be formed at the dissolving surface and drug will need to pass this layer on its way to the bulk phase [29, 30]. In this study, we have used different ionic nature polymers and weakly basic BOS particles are expected to get dissolved in this layer of anionic polymers (carrier controlled mechanism). However, the drug-controlled release mechanism cannot be underestimated alluding towards the amorphosization of the drug particles and particle size reduction. As BOS is poorly soluble in nature it may be assumed that the hike in the drug release is the result of interplay of both the mechanisms. It is also likely that the solid dispersions with reasonable concentration of polymer, the diffusion layer contain the polymers and the increased dissolution rate of BOS could be related to an increased solubility of BOS in the dissolving surface. The ultimate success of a solid dispersion is determined by its performance in dissolution after oral administration. Furthermore, the probability of crystallization might be decreased by the presence of polymer, as the polymer hinders the BOS molecules to form seeds/nuclei. This is suitably explained by “spring-and-parachute” concept. The general strategy behind almost all solubilisation technologies is the so called “spring-and-parachute” concept [37]. Generally, supersaturable formulations are able to induce state of supersaturation when exposed to the

aqueous environment of the gastrointestinal tract. However, in order to have effective therapeutic outcome, supersaturation must be generated and maintained for drugs to be absorbed in the desired time frame. The concept of generation and maintenance of a supersaturated state is commonly described by this theory. 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 GI tract. Drugs in this state have a tendency to precipitate rapidly before being absorbed resulting in reduced bioavailability. The maintenance of the drug in the solution stage for reasonable time frame results in effective oral absorption from the formulation [37, 38]. In the development aspects of solid dispersion formulations, the performance of the formulation depends on many factors like processing techniques used, physicochemical properties of the compound and the tendency to form and maintain a supersaturated drug solution. A variety of polymer excipients have been evaluated for their ability to prolong the supersaturation and inhibit drug precipitation [38]. The formulation design aspects of the solid dispersion rely upon criticality of selection of a suitable carrier which determine dissolution aspects and while choosing a carrier drug-carrier solubility and compatibility has to be considered [35]. Drug-carrier incompatibility and lack of drug-carrier solubility result in phase separation in the form of amorphous or crystalline drug precipitates resulting in formulation failure. Such phase separation and crystallization problems are faced with ageing, where drug-carrier solubility is not appreciable. Of course, the kinetic immobilization of the supersaturated drug concentrations into a highly viscous matrix should prevent phase separation and crystallization. Many researchers have reported the utilization of 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, HPMCP HP 55 and HPMC AS MF(anionic), Eudragit® EPO (cationic) and Povidone K 30 (non-ionic) to evaluate the effect of the polymers in maintaining a supersaturated BOS concentration in the dissolution medium. It was observed that the solid dispersions of BOS with Eudragit® L 100 55, HPMCP HP 55 and HPMC AS MF 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 [39, 40] or, suppressing the nucleation process [41] or, adsorbing on the surface of crystals to block the access of solute molecules ("the poisoning effect") thus preventing or, retarding crystal growth [42, 43]. It is evident from the *in-silico* studies that these anionic polymers interacts with BOS which may be driven by hydrogen bond formation and/or hydrophobic interactions resulting in the inhibition of nucleation and recrystallization [44, 45, 46].The process of delaying of nucleation and inhibition of recrystallization may not be only due to the increase in the nucleation activation energy but also reduction of crystal growth [47, 48, 49]. The interaction *via* hydrogen bonding

between the carboxyl group of the anionic polymers 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. As besides this interaction, inhibition of the crystallization is resultant of various other factors like lipophilicity of the polymers, rigidity of the polymers, adsorption onto the crystal surface resulting in steric hindrance and few other factors [50-57]. Dissolution profiles of solid dispersions with these anionic polymers 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 these anionic polymers 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. It is evident from the dissolution study that the supersaturation of BOS was effectively prolonged in the presence of such polymers. In the release mechanism of drug from the solid dispersions, it may also be considered that dissolution of drug and polymer in the solid dispersion occur 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. Nevertheless, another mechanism associated in the dissolution process of the solid dispersions is the formation of various structures during this dissolution process like free drug, 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 [58]. We have attempted to achieve pH-independent release of BOS from polymeric matrices by incorporation of polymers of different ionic characteristics to compare the release behaviour. The solid dispersions prepared with the anionic polymers 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 these polymers to 0.1N HCl, significant improved release behaviour was observed for the solid dispersions with Eudragit® L 100 55, HPMCP HP55 and HPMC AS MF than the solid dispersions prepared from Eudragit® EPO and Povidone K30. This may be assumed that BOS molecules could have been solubilized due to the acidity of the anionic polymers and got released completely. Further, porosity of the solid dispersion and presence of SLS could have aided the drug release under different conditions and might have been synergistic factors towards the BOS release from the solid dispersions. In the case of many partially crystalline solid dispersions, BOS has shown small crystalline peaks in the diffractogram, but the BOS release is appeared to be high. Thus, these forms also appear to aid in creation of supersaturated state that is subsequently stabilized by the polymer. On administration of a nanocrystal, formulation particles are released in the nano-range, which is of paramount importance in imparting many advantages to the nanocrystals, *viz* fast dissolution, increased kinetic saturation solubility and adhesion to biological membranes, which ultimately results in enhanced solubility and permeability. Nano-sization of the particles

results in a decreased particle size thereby increasing surface area that ultimately leads to a substantial augmentation in both, the curvature of the particle and interface available for interaction with the surroundings. Increased curvature results in higher dissolution pressure, which favours the dissolution of the molecules at the crystal surface, consequentially increasing kinetic saturation solubility [59, 60, 61]. Both of the above factors result in increased flux across the gut lumen and to the blood. We have attempted four novel techniques like solvent controlled coprecipitation, fusion, nanoprecipitation and spray drying 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. The discussed drug-polymer interaction through hydrogen bonding or, any other electrostatic interaction could have resulted 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. 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 higher than BOS itself (37%) and is attributed to the molten stringent polymer matrix locking the BOS particles. The release behaviour indicate solubilization is related to the ionic nature of the polymer. The polymer-specific properties of the anionic polymers prolonged supersaturation by increasing media viscosity and interaction with BOS are attributing for the inhibiting behaviour against crystallization.

Table 1. Physico-chemical characterization and micromeritics properties of solid dispersions of bosentan.

S. No.	Technology	Polymer	Ratio	Sample Code	Yield (%)	MC (%)	Assay (%)	Compressibility property				% P	AR (°)
								BD (g/mL)	TD (g/mL)	CI (%)	HR		
1	NA	NA	NA	BOS	NA	3.17	99.80	0.21	0.26	19.08	1.24	37.36	40.00
2	**Solvent controlled coprecipitation**	Eudragit L 100 55	R 1:1	BCPL1	60.00	2.61	96.73	0.25	0.31	20.00	1.25	68.63	30.00
3			R 1:2	BCPL2	68.33	2.29	95.27	0.25	0.29	15.00	1.18	70.40	32.00
4			R 1:3	BCPL3	86.25	2.28	96.85	0.24	0.30	20.39	1.26	70.50	32.00
5		Eudragit EPO	R 1:1	BCPE1	62.50	2.35	93.45	0.24	0.31	23.81	1.31	70.99	33.00
6			R 1:2	BCPE2	65.00	1.90	93.82	0.24	0.29	19.05	1.24	71.85	33.00
7			R 1:3	BCPE3	90.00	2.72	97.33	0.24	0.29	19.05	1.24	71.42	34.00
8		PVPK30	R 1:1	BCPP1	45.00	2.78	92.00	0.23	0.31	27.27	1.38	71.45	30.00
9			R 1:2	BCPP2	53.33	2.87	93.58	0.23	0.31	27.27	1.38	71.89	30.00
10			R 1:3	BCPP3	72.50	3.02	97.82	0.25	0.31	20.00	1.25	69.52	30.00
11		HPMCP HP 55	R 1:1	BCPHP1	63.75	1.98	96.36	0.25	0.31	20.00	1.25	69.07	30.00
12			R 1:2	BCPHP2	68.33	2.58	95.15	0.25	0.31	20.00	1.25	68.62	32.00
13			R 1:3	BCPHP3	85.88	2.88	97.33	0.25	0.31	20.00	1.25	69.52	32.00
14		HPMC AS MF	R 1:1	BCPAS1	62.50	2.05	93.58	0.25	0.31	20.00	1.25	69.98	32.00
15			R 1:2	BCPAS2	70.00	3.22	95.15	0.25	0.31	20.00	1.25	69.52	32.00
10			R 1:3	BCPAS3	88.75	3.25	97.33	0.25	0.31	20.00	1.25	68.62	33.00
11	**Fusion**	Eudragit L 100 55	R 1:1	BHML1	83.33	1.50	96.48	0.36	0.45	21.43	1.27	54.91	25.00
12			R 1:2	BHML2	92.78	1.70	95.27	0.42	0.50	16.67	1.20	50.89	25.00
13			R 1:3	BHML3	90.83	1.85	98.91	0.42	0.50	16.67	1.20	49.16	24.00
14		Eudragit EPO	R 1:1	BHME1	80.00	1.40	96.48	0.33	0.42	20.00	1.25	59.35	25.00
15			R 1:2	BHME2	94.00	1.45	96.61	0.36	0.42	14.56	1.17	58.11	25.00
16			R 1:3	BHME3	93.33	2.00	97.58	0.38	0.50	23.08	1.30	53.92	25.00
17		PVPK30	R 1:1	BHMP1	78.33	1.60	90.18	0.36	0.42	14.29	1.17	54.86	26.00
18			R 1:2	BHMP2	91.89	1.80	90.30	0.37	0.45	19.26	1.24	54.45	25.00
25			R 1:3	BHMP3	95.17	2.21	97.70	0.42	0.50	16.67	1.20	49.16	27.00
26		HPMCP HP 55	R 1:1	BHMHP1	77.50	1.40	97.70	0.36	0.42	14.29	1.17	55.65	26.00
27			R 1:2	BHMHP2	85.11	1.65	96.36	0.38	0.45	17.06	1.21	52.37	28.00
28			R 1:3	BHMHP3	94.08	2.10	96.73	0.42	0.50	16.67	1.20	49.16	25.00
29		HPMC AS MF	R 1:1	BHMAS1	81.67	1.50	90.30	0.33	0.42	20.00	1.25	60.05	25.00
30			R 1:2	BHMAS2	93.33	1.62	97.33	0.38	0.45	15.38	1.18	53.07	25.00
31			R 1:3	BHMAS3	95.83	1.92	90.18	0.38	0.45	15.38	1.18	51.41	25.00

S. No.	Technology	Polymer	Ratio	Sample Code	Yield (%)	MC (%)	Assay (%)	Compressibility property				% P	AR (°)
								BD (g/mL)	TD (g/mL)	CI (%)	HR		
32	Nanoprecipitation	Eudragit L 100 55	R 1:1	BNPL1	50.00	2.50	93.45	0.25	0.31	19.00	1.23	68.44	32.00
33			R 1:2	BNPL2	63.33	2.80	94.79	0.28	0.31	10.00	1.11	67.26	32.00
34			R 1:3	BNPL3	76.25	2.85	98.30	0.28	0.31	10.56	1.12	66.11	32.00
35		Eudragit EPO	R 1:1	BNPE1	55.00	2.70	93.70	0.24	0.30	20.48	1.26	70.96	33.00
36			R 1:2	BNPE2	68.33	2.75	96.61	0.27	0.30	10.81	1.12	68.20	32.00
37			R 1:3	BNPE3	77.50	2.71	97.58	0.27	0.31	11.41	1.13	67.45	31.00
38		PVPK30	R 1:1	BNPP1	55.00	2.60	95.88	0.25	0.31	20.00	1.25	68.40	32.00
39			R 1:2	BNPP2	60.00	2.84	95.27	0.28	0.31	11.11	1.13	65.52	33.00
40			R 1:3	BNPP3	68.75	2.90	96.00	0.28	0.32	12.50	1.14	66.11	32.00
41		HPMCP HP 55	R 1:1	BNPHP1	52.50	2.42	92.97	0.267	0.316	15.51	1.18	66.80	31.00
42			R 1:2	BNPHP2	58.33	2.49	97.33	0.275	0.329	16.48	1.20	65.29	32.00
43			R 1:3	BNPHP3	72.50	2.51	93.94	0.275	0.329	16.48	1.20	66.48	31.00
44		HPMC AS MF	R 1:1	BNPAS1	60.00	2.71	96.48	0.238	0.299	20.48	1.26	71.46	32.00
45			R 1:2	BNPAS2	63.33	2.75	95.27	0.270	0.303	10.81	1.12	67.02	31.00
46			R 1:3	BNPAS3	73.75	2.77	90.18	0.272	0.307	11.41	1.13	65.67	32.00
47	Spray drying	Eudragit L 100 55	R 1:1	BSDL1	62.50	1.91	92.97	0.161	0.208	22.58	1.29	79.64	40.00
48			R 1:2	BSDL2	70.00	2.11	96.24	0.167	0.217	23.33	1.30	80.35	42.00
49			R 1:3	BSDL3	87.50	2.15	94.06	0.167	0.217	23.33	1.30	79.66	41.00
50		Eudragit EPO	R 1:1	BSDE1	60.00	1.92	95.15	0.143	0.227	37.14	1.59	82.58	45.00
51			R 1:2	BSDE2	68.33	2.21	93.45	0.152	0.227	33.33	1.50	82.17	46.00
52			R 1:3	BSDE3	88.75	2.20	97.33	0.161	0.208	22.58	1.29	80.68	45.00
53		PVPK30	R 1:1	BSDP1	55.00	1.95	92.97	0.152	0.208	27.27	1.38	80.85	45.00
54			R 1:2	BSDP2	71.67	1.98	93.58	0.156	0.217	28.13	1.39	80.61	45.00
55			R 1:3	BSDP3	90.00	2.11	92.24	0.156	0.217	28.13	1.39	80.93	45.00
56		HPMCP HP 55	R 1:1	BSDHP1	62.50	1.91	93.58	0.143	0.227	37.14	1.59	82.26	45.00
57			R 1:2	BSDHP2	75.00	2.24	94.55	0.143	0.227	37.14	1.59	81.95	45.00
58			R 1:3	BSDHP3	88.75	2.24	94.06	0.152	0.227	33.33	1.50	81.51	45.00
59		HPMC AS MF	R 1:1	BSDAS1	70.00	1.96	93.58	0.152	0.208	27.27	1.38	81.84	45.00
60			R 1:2	BSDAS2	73.33	2.10	91.52	0.156	0.217	28.13	1.39	80.93	45.00
61			R 1:3	BSDAS3	92.50	2.14	95.64	0.156	0.217	28.13	1.39	80.26	45.00

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

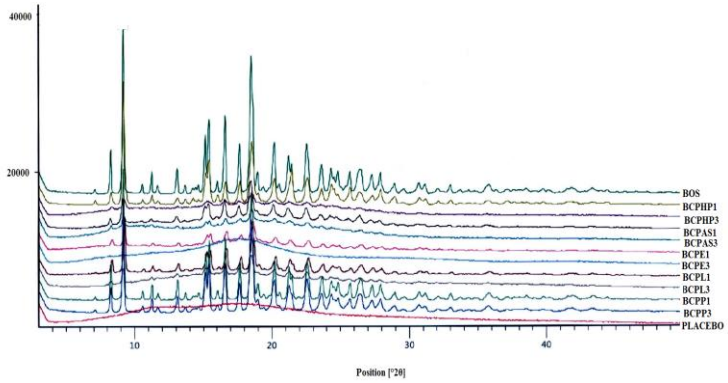
Table 2. Characteristics of different preparations of dispersions from bosentan in Milli Q water by nanoprecipitation technique.

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	479.2	0.794
		R 1:3	BNPP3	254.8	0.198
4	HPMCP HP 55	R 1:1	BNPHP1	54.8	0.172
		R 1:2	BNPHP2	489.3	0.186
		R 1:3	BNPHP3	550.2	0.178
5	HPMC AS MF	R 1:1	BNPAS1	56.8	0.196
		R 1:2	BNPAS2	505.8	0.753
		R 1:3	BNPAS3	553.2	0.339

Table 3. Statistical treatment to the dissolution profile of respective solid dispersions of BOS with HPMCP HP 55 prepared by different techniques.

	f_1					f_2				
Dissolution medium	**BOS**	**BCPE3**	**BCPP3**	**BCPL3**	**BCPAS3**	**BOS**	**BCPE3**	**BCPP3**	**BCPL3**	**BCPAS3**
0.1 N HCl	93.05	75.33	66.19	41.23	5.68	4.47	8.81	11.60	20.54	63.14
pH 6.8 phosphate buffer	95.35	85.82	73.86	9.86	4.65	3.13	5.39	8.40	38.82	67.50
	BOS	**BHME3**	**BHMP3**	**BHML3**	**BHMAS3**	**BOS**	**BHME3**	**BHMP3**	**BHML3**	**BHMAS3**
0.1 N HCl	92.78	73.08	74.74	13.16	5.57	4.92	9.41	9.61	41.43	61.24
pH 6.8 phosphate buffer	95.07	84.03	76.65	13.42	4.8	3.85	6.65	8.69	42.84	65.74
	BOS	**BNPE3**	**BNPP3**	**BNPL3**	**BNPAS3**	**BOS**	**BNPE3**	**BNPP3**	**BNPL3**	**BNPAS3**
0.1 N HCl	91.59	72.51	52.02	7.27	4.21	8.32	11.39	14.69	54.32	67.54
pH 6.8 phosphate buffer	94.84	75.28	72.79	14.01	3.71	5.56	10.45	11.36	40.43	71.39
	BOS	**BSDE3**	**BSDP3**	**BSDL3**	**BSDAS3**	**BOS**	**BSDE3**	**BSDP3**	**BSDL3**	**BSDAS3**
0.1 N HCl	93.96	65.32	71.35	38.24	33.05	1.54	9.29	7.45	17.46	20.84
pH 6.8 phosphate buffer	95.33	89.43	73.80	14.04	9.32	2.71	4.07	8.37	37.16	48.31

A



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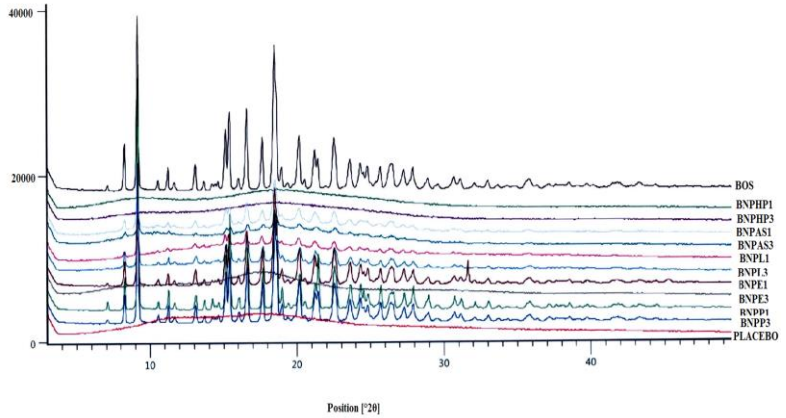

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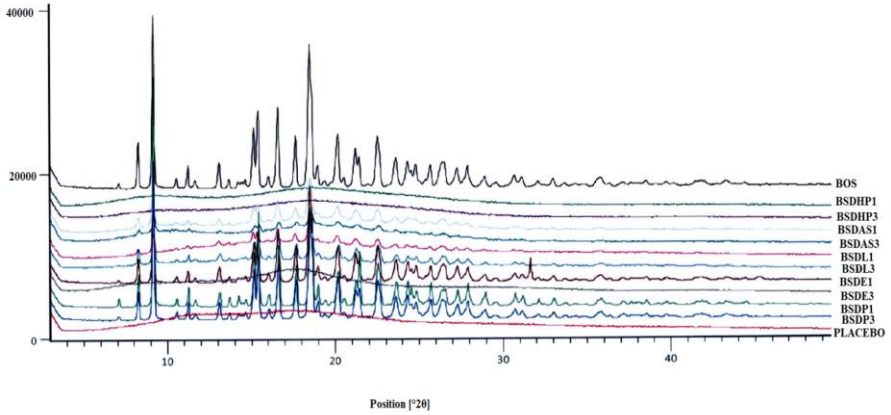

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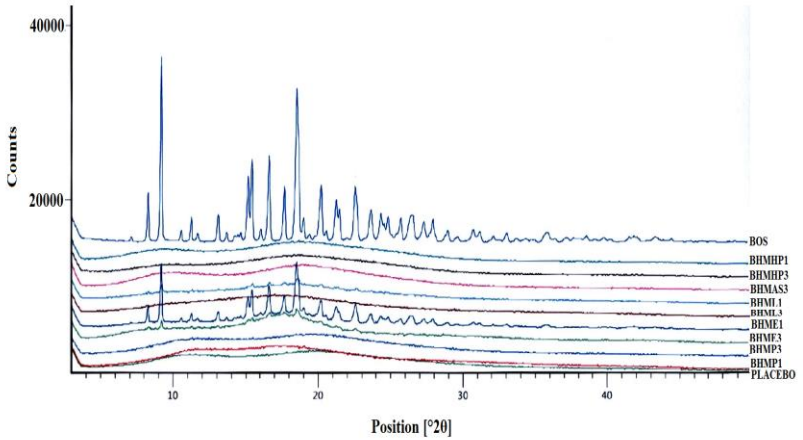

Figure 1. X-ray powder diffraction pattern summarizing the comparative diffractogram of BOS, placebo and different solid dispersions prepared by (A) solvent controlled coprecipitation technique, (B) nanoprecipitation technique (C) fusion technique (D) spray drying technique.

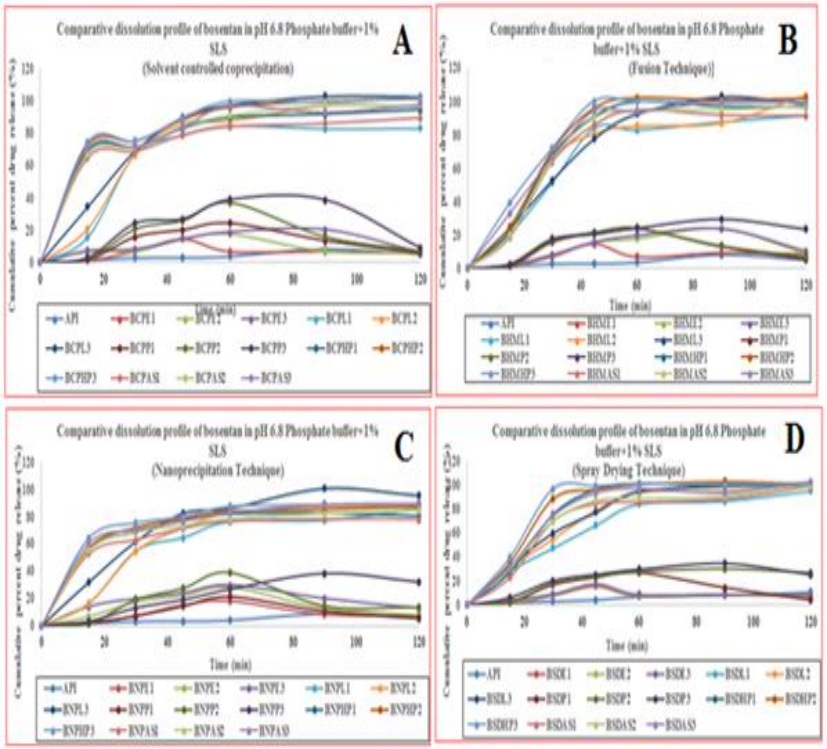

Figure 2. Cumulative release of BOS from solid dispersions by (A) solvent controlled coprecipitation technique, (B) fusion technique (C) nanoprecipitation technique (D) spray drying technique in 0.1 N HCl + 1% w/v SLS. Each value represents the mean ± SD, (n=3).

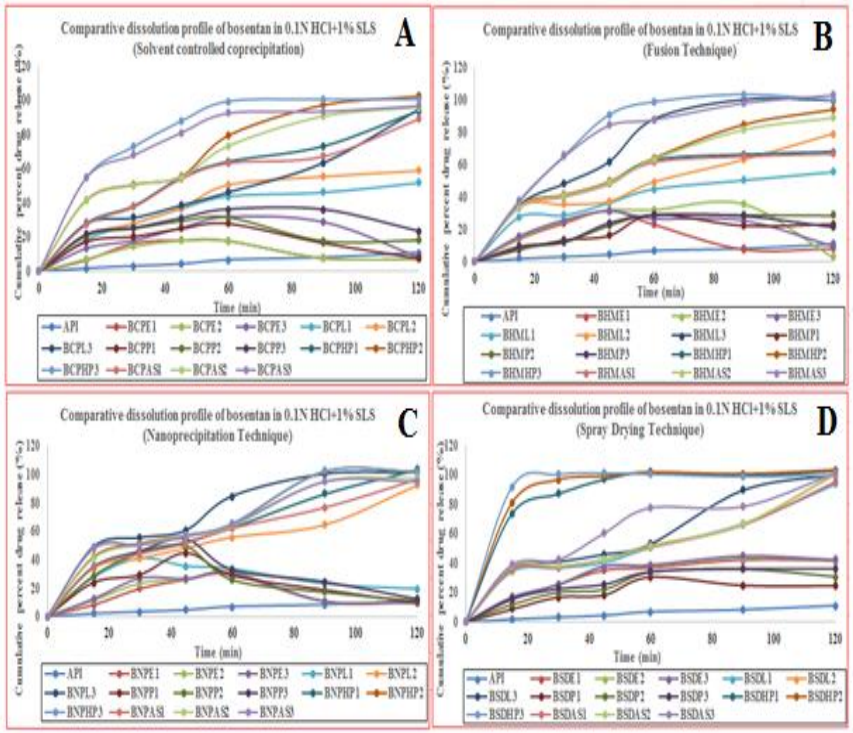

Figure 3. Cumulative release of BOS from solid dispersions by (A) solvent controlled coprecipitation technique, (B) fusion technique (C) nanoprecipitation technique (D) spray drying technique in 0.067 M Phosphate Buffer, pH 6.8 + 1% w/v SLS. Each value represents the mean ± SD, (n=3).

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 and in their development scientists are succeeding in resolving the stability issues of such preparations. These results emphasize that mechanisms of supersaturation could differ significantly depending on the specific drug-polymer combination and judicious selection of polymer and optimizing the concentration may result in viable formulation design with optimal therapeutic outcome.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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