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Research Article

Effect of Polyethylene Glycol and PVP K-30 on the Solubility and Dissolution Rate Enhancement of Antihypertensive Drug Irbesartan

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ABSTRACT

Aim and objective: The study was aimed to improve the dissolution rate of poorly water-soluble drug irbesartan (IBS). Methods: The effects of PEGs (4000, 6000 and 8000) and PVP K-30 and methods of preparations in different ratios on dissolution behaviour of IBS were investigated. Selected formulations were characterized by FTIR, DSC. Results and discussion: FTIR and DSC showed the compatibility with the polymers. The significant change in melting pattern of the IBS observed in the DSC signified the transition to amorphous state. PEG 8000 based SD (1:5 w/w, SEM) showed significant enhancement of dissolution. Conclusion: It was concluded that SEM method and PEG 8000 as carrier were most suitable for the enhancement of the dissolution. This is an alternative approach for the enhancement of solubility and dissolution rate.

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INTRODUCTION

Irbesartan (IBS) is an angiotensin II type I receptor antagonist. It is used as antihypertensive agents alone or with other for management of cardiovascular diseases (1, 2). IBS is commercially available as tablets. The recommended dose of IBS for treating hypertension is 75 to 300 mg once daily. Solubility of IBS is (0.00884 mg/mL) signifies practically insoluble in water (BCS class II) with 60-80% oral bioavailability (3). The aqueous solubility of the drug leads to poor bioavailability, so the small amount of drug present in the small intestine. Thus, to increase the bioavailability of BCS class II drug in gastrointestinal needs to improve the solubility of those compounds. Various methods are proposed to enhance aqueous solubility of poorly soluble drugs that includes: chemical modifications (e.g., pro drugs or salt derivatives), physical modifications (e.g., solid dispersions, size reduction, loading on porous carriers, co crystals), alteration of solvent compositions (e.g., pH adjustment, use of co solvents, addition of surfactants), and use of carrier systems (e.g., cyclodextrins, micelles, liposomes). Among various techniques, solid dispersions of drugs have been the most successful approach (4). Many techniques have been exercised for the enhancement of dissolution and improve bioavailability of poorly water-soluble drugs like IBS, such as particle size reduction (5), SD (6-8) and inclusion in cyclodextrins (5-9). SDs are mixture of the drug and the hydrophilic polymer where both are molecularly mixed (10). SD system is a well- established method has attracted attention of the researchers for previous 50 years. Several methods such as melting/fusion (FM), solvent evaporation (SEM), solvent wetting, and physical mixing (PM) methods were previously reported to prepare the SDs (11-17). In SD system, there is improvement of wettability of drug, particle size reduction and high surface area helps to increase solubility of drug (11).

Many carriers like polaxamer, gelucire, polyethylene glycols (PEGs), sodium carboxymethyl cellulose, povidone, crospovidone, microcrystalline cellulose, polymethacrylate, chitosan are used to obtain SDs (16-20) but it's had own advantages and limitations. The nature of carriers typically influences the type of method for preparations of SDs. PEGs are polymers of ethylene oxide available in different grades, with molecular weight ranges from 200 to 30,000. PEGs are commonly used for their good solubility nature in water and in many organic solvents, low melting point,

low toxicity, improving drug wettability, hydropholicity and wide drug compatibility. PEGs with molecular weight 1500-20,000 and melting point range 33-65ºC are used for the manufacture of SD (11, 21, 22).

The purpose of the present study is to characterize the solid-state of the SD system of IBS in PEG 4000, PEG 6000, PEG 8000 and PVP K-30 prepared by PM, SEM, FM at different weight ratios. SD was characterized using Flourier transfer infrared spectroscopy (FTIR), Differential scanning calorimetry (DSC).

MATERIALS AND METHODS

Materials

IBS, a gift sample from Piramal Health care, Mumbai, India. PEGs and PVK-30 were provided by Yarrow Chem Products, Mumbai, India. All other chemicals and reagents were of analytical grade of purity.

Method

Phase solubility studies

Drug was added in excess to 25 ml of distilled water containing various concentrations (1%, 2%, 4%, 6%, 8%, 10% w/v) of PEG's (4000, 6000, 8000) and PVP K-30 in a series of glass vials. These mixtures were shaken on a water bath shaker at 37 ºC for 48 h in order to achieve equilibrium solubility. Samples were filtered using Whatman no.1 filter paper. Filtrate after dilution was analyzed using a spectrophotometer (230 nm, Aligent Cary 60). Phase solubility studies were conducted with and without the addition of hydrophilic carrier. The solubility experiments were performed in triplicate.

The Gibb's free energy of transfer (ΔG_{tr}^{o}) of IBS from pure water to the aqueous solution of carriers by using below equation

$$\Delta G_{tr}^{o} = -2.303\ RT \log S_o/S_s$$

Where,

S_o/S_s is the ratio of molar solubility of drug in aqueous solutions of carriers to that of the pure water.

Preparation of PMs and SDs

SD of IBS with different hydrophilic carriers like PEG's 4000, 6000, 8000 and PVP K-30 were prepared by PM, SEM and FM.

PM

The PMs of IBS with the carrier (PEGs 4000, 6000, 8000 and PVK-30) were prepared separately at four different weight ratios of 1:1, 1:3, 1:5 and 1:7. Homogenous mixture was resulted after 10 m of mixing in a motor and pestle.

SEM

In this method SDs were prepared using drug to carrier weight ratios 1:1, 1:3, 1:5 and 1:7. Individually IBS and carriers were dissolved in 10 mL of methanol with assist of magnetic stirrer (1 h, 25 °C). Methanol was removed at 40 ºC using hot air oven until it evaporated.

FM

SDs were prepared at 1:1, 1:3, 1:5 and 1:7 (weight ratios). Individual carrier was heated above its melting point. Measured quantity of IBS was added to the individual molten carrier. with continuous stirring. The system was cooled rapidly in an ice bath containing sodium chloride for 3 h.

The resulting mixtures of PM, SEM and FM were passed through # 40. Individual mixture was packed in screw cap vial and stored in desiccator for further experiments (23, 24).

Table 1: Preparation of the PM and SDs with different methods using different molecular weight of PEG and PVK-30 (23, 24).

Formulation code	Polymer used	Drug: polymer	Method of preparation
L - 1	PEG-4000	1:1	PM
L – 2		1:3	
L – 3		1:5	
L – 4		1:7	
L – 5	PEG-4000	1:1	SEM
L – 6		1:3	
L – 7		1:5	
L – 8		1:7	
L – 9	PEG-4000	1:1	FM
L – 10		1:3	
L – 11		1:5	
L – 12		1:7	
L – 13	PEG-6000	1:1	PM
L – 14		1:3	
L – 15		1:5	
L – 16		1:7	

L – 17	PEG-6000	1:1	SEM
L – 18		1:3	
L – 19		1:5	
L – 20		1:7	
L – 21	PEG-6000	1:1	FM
L – 22		1:3	
L – 23		1:5	
L – 24		1:7	
L – 25	PEG-8000	1:1	PM
L – 26		1:3	
L – 27		1:5	
L – 28		1:7	
L – 29	PEG-8000	1:1	SEM
L – 30		1:3	
L – 31		1:5	
L – 32		1:7	
L – 33	PEG-8000	1:1	FM
L – 34		1:3	
L – 35		1:5	
L – 36		1:7	
L – 37	PVP K-30	1:1	PM
L – 38		1:3	
L – 39		1:5	
L – 40		1:7	
L – 41	PVP K-30	1:1	SEM
L – 42		1:3	
L – 43		1:5	
L – 44		1:7	

Drug content

A specified weight of each mixture was dispersed in 50 ml of methanol by aid of magnetic stirring for 30 m. Dispersions were filtered through Whattman filter paper and the absorbance was measured

spectrophotometrically after appropriate dilution.

Solubility determination

An excess quantity of prepared mixture was placed in the 0.1N HCl. The mixtures were shaken for 48 h at 37ºC in a water bath shaker. Supernatant was filtered after one hour through a Millipore filter (pore size 0.45µm). Assayed spectrophotometrically after suitable dilution.

FTIR

FTIR spectrums of samples were recorded by infrared spectrophotometer (Shimadzu IR-435, Kyoto, Japan) over a scanning range of 4,500-500 cm^{-1}.

DSC

DSC thermograms of samples were recorded by differential scanning calorimeter (Pyris Diamond, PerkinElmer, Singapore). The samples were crimped using a TA crimper and heated at 10 ºC/m over a temperature range of 20-250 ºC and nitrogen flow rate of 25 mL/m.

In vitro dissolution

Dissolution was performed in triplicate for pure drug and prepared samples using USP II, TDT-08L, Electrolab, Mumbai dissolution test apparatus. An equivalent to 150 mg of the IBS was taken. Simulated gastric medium (0.1 N HCl, 900 mL) maintained at 37 ± 0.5 ºC with 50 rpm was selected for this dissolution. Samples (5 mL) were withdrawn at predetermined sampling intervals (5, 10, 15, 30, 45, 60, 120 m). The volume was maintained constant throughout the test. Withdrawn samples were analysed spectrophotometrically after suitable dilution.

RESULTS AND DISCUSSION

Phase solubility studies

Phase solubility showed an increase in solubility of IBS with increase in concentration of each of the carriers (PEG's 4000, 6000, 8000 and PVP K-30). An indication of the process of transfer of drugs from pure water to the aqueous solutions of carriers was obtained from the values of Gibb's free energy change. The obtained values of Gibb's free energy provided the information regarding the increased solubility of the drug in the presence of polymer. ΔG_{tr}°C values were the entire negative for the polymers at different concentrations, i.e., indicating the spontaneous nature of drug's solublization and it increases its value with an increase in its concentration. So that the reaction became more favourable as the concentration of polymer increased (25).

Table 2: Thermodynamic parameters of the solubility process of IBS in different carrier-water solutions at 37 °C.

% (w/v) of carrier in water	Gibb's Free Energy $\Delta G°_{tr}$ (J/mol)			
	PEG 4000	**PEG 6000**	**PEG 8000**	**PVP K-30**
1	-2077.52	-1580.83	-2110.63	-2845.38
2	-3618.96	-2267.63	-2951.57	-2212.25
4	-3950.08	-2762.03	-3376.89	-2559.36
6	-4654.58	-3410.58	-5697.05	-3009.80
8	-4759.05	-3647.50	-6354.16	-4123.07
10	-5688.49	-3744.56	-7027.83	-4938.89

Formulation of the PMs and SDs and optimization of the ratios and methods

There are 44 formulations were developed using PEGs and PVK. PM, SEM and FM was adopted to formulate the products at various drug and carrier weight ratios. Transition from crystalline IBS to amorphous leads to the enhancement of IBS solubility and dissolution. In case of PEGs and PVK-30, solubility of IBS significantly increased proportionally. Weight ratio of 1:5 showed higher dissolution than the other weight ratios. PEG 8000 at 1:5 weight ratios prepared by SEM showed highest solubility than the other polymers and methods. The significant increase in solubility of IBS in PEG 8000 may be due to their surface-active nature and wetting behavior (26).

The drug content of the PMs and SDs of the PEGs and PVK K-30 ranged between 93.46 to 97.39 and 91.62 to 96.81 % respectively. This suggests chosen methods are reliable and reproduced that the methods used for preparation of formulations were reliable and reproducible.

FTIR

The FTIR spectra of pure drug IBS, carriers and formulations of IBS are depicted in Fig. 1. The FTIR spectra of IBS showed characteristics absorption of N-H stretching vibration at 3055.24 cm^{-1}, C-H streching vibration at 302960.73 cm^{-1},

C=O stretching vibration at 1701.22 cm^{-1} and C=N stretching vibration at 1685.79 cm^{-1} (27). The characteristic peaks of C-H (stretch) at 2955.07 cm^{-1}, C-O (stretch) at 1733.12 cm^{-1} is assigned to spectrum of PEG-8000. The spectrum of PVPK-30 showed bands at 1711.90 cm^{-1} (C=O stretch) in the cyclic amide and a broad band at 2882.70 cm^{-1}attributes to aliphatic C-H stretch. There is no sign of chemical interaction from the formulation spectra. All formulae displayed all characteristic peaks of their respective components at the same position appearing for each constituent when analyzed alone. The shifting of 1701.22 cm^{-1} to 1684.46 cm^{-1} indicated the intermolecular interaction of IBS and carrier. This might be responsible for the enhancement of solubility and dissolution rate of the IBS.

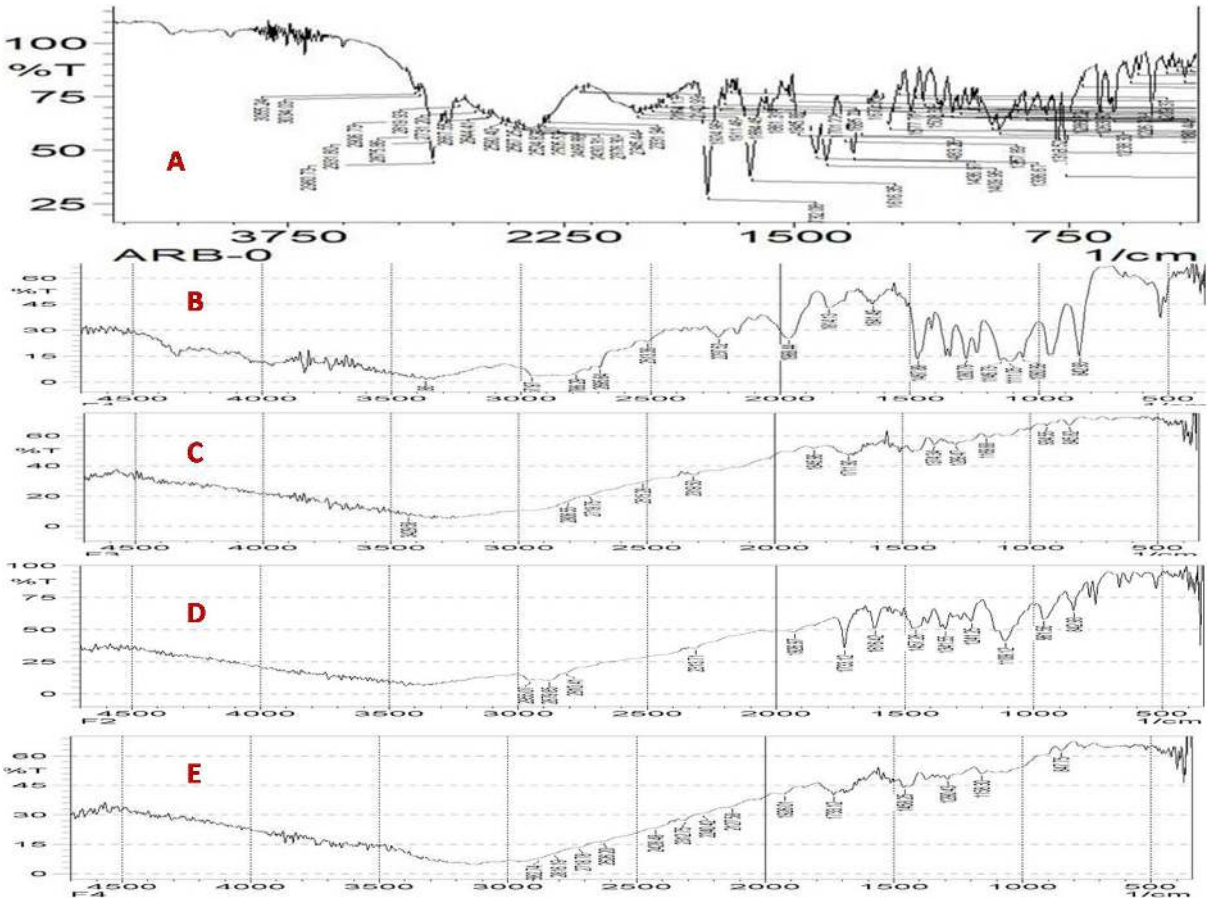

Fig. 1 FTIR spectra of (A) IBS, (B) PEG 8000, (C) PVP K-30, (D) PEG 8000 based SD prepared by SEM at weight of 1:5, (E) PVP K-30 based SD prepared by SEM at weight ratio of 1:5.

DSC

DSC thermogram of pure drug IBS, carriers and different formulations of IBS are presented in Fig. 2. The DSC thermogram of IBS showed presence of a sharp endothermic peak at 184.9°C (29) assigned the melting point of IBS. The measured melting endotherms for PEG-8000 and PVP K-30 are observed at 79.91°C and 168.49 °C, respectively. In the thermograms of SD's the melting endotherms of PEG 8000 are almost unchanged and PVP K-30 was there is a broad peak with more intensity. With addition of PEG-8000 in the SDs at 1:5 w/w, the melting peak of IBS becomes shorter and broader. Indicating the presence of drug in amorphous form and there is a significant interaction between the drug and polymer. In DSC thermogram of PVP K-30, presences of asymmetric peak with more intensity were observed which indicated the presence of amorphous form is also associated with the enhanced solubility.

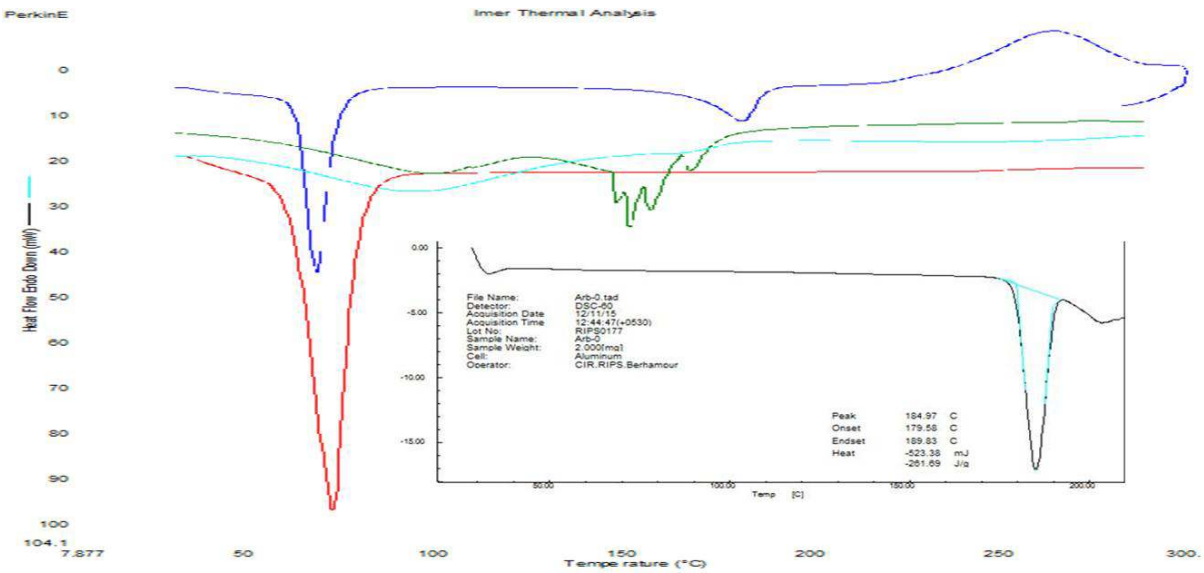

Fig. 2 DSC thermographs of IBS (insert-black), PEG 8000 (red), PVP K-30 (green), (D) PEG 8000 based SD prepared by SEM at weight of 1:5 (blue), PVP K-30 based SD prepared by SEM at weight ratio of 1:5 (Sky colour).

In vitro dissolution studies

The dissolution profiles of IBS, formulations of PEGs and PVP K-30 were depicted in the Fig. 2. Crystalline IBS showed an incomplete release (54.57 ± 2.56 %) after 75 min of dissolution. PEG 6000 based PM (1:5 w/w) showed better drug release (96.60%) when compared to

SDs prepared in FM and SEM in different ratios. Dissolution rates of SD formulation containing PEG 8000 were higher than those for the PM, FM and IBS alone. The PEG 8000 based SD (SEM) at 1:5 showed 98.19 % drug release within 60 min of dissolution. The PVP K-30 based PM showed higher drug release than (97.30 %) than other formulation ratios and methods used in same polymers. All the SD's formulation exhibited higher rate of dissolution than the pure drug. The dissolution was significantly ($p < 0.05$) higher than that of pure drug. Difference factor ($f_1 = 123.82$) and similarity factor ($f_2 = 24.55$) were calculated between the IBS and PEG 8000 (1:5 w/w, SEM). The f_1 value more than 15 and f_2 value less than 50 showed that IBS and PEG 8000 (1:5 w/w, SEM) product were not equivalent. It demonstrated a significant difference in dissolution data between PEG 8000 (1:5 w/w, SEM) and pure drug IBS. This might be due to the change in the state of the drug from the crystalline to amorphous, increase in wettability and prevention of aggregation of the drug particles by carriers (23). Simple PM of the drug with the hydrophilic carriers increased the solubility of drug to some extent but formulation of SDs by SEM and FM, for the improvement of further dissolution rate of the drug.

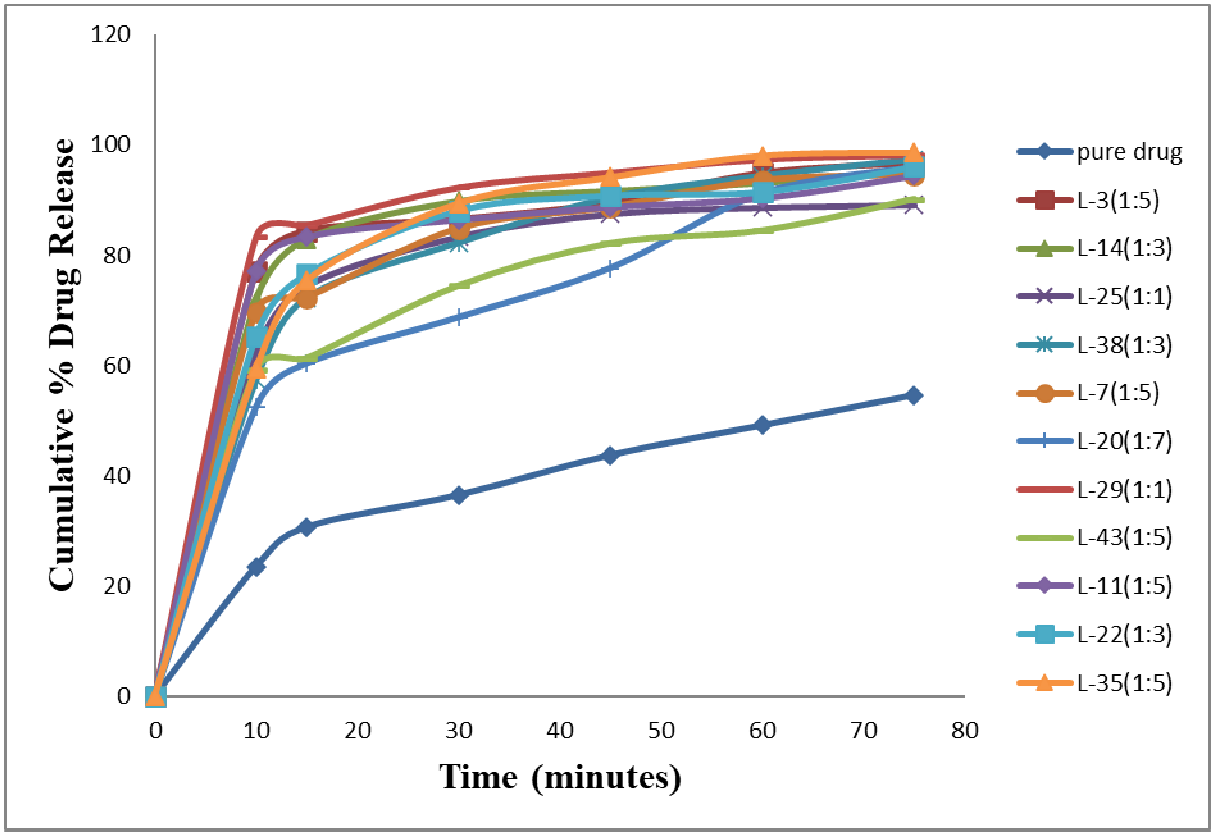

Fig. 3 Dissolution profiles of the IBS formulations prepared by the different molecular weight PEGs and PVP K-30 and in various methods.

CONCLUSIONS

The different technique available for solubility enhancement, preparation of SDs has been the most successful strategy. The increase in solubility may be contributed due to reduction of particle aggregation of the drug, increased wettability and alteration of surface properties of drug from its SD's. SDs prepared by SEM exhibited higher dissolution rates. The dissolution enhancing effect of various carriers used in this study followed the given order: PEG 8000 > PEG 4000 > PEG 6000 > PVP K-30. In this revealed the suitability of the SEM for formation of amorphous SDs of IBS. Higher dissolution of IBS by this formulation signifies the suitability. It is an alternative approach for the enhancement of solubility hence dissolution and bioavailability. This may also extended to other drugs for the enhancement of solubility.

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