Original Article

Improved Dissolution and Bioavailability of Eprosartan Mesylate Formulated as Solid Dispersions using Conventional Methods

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ABSTRACT

Background: Eprosartan mesylate (EM) is a poorly aqueous soluble drug belonging to BCS-class II suffers from low bioavailability (13%). The present study involves an effort for improving dissolution and thus the bioavailability of EM using solid dispersion approach. **Methods:** Solid dispersion (SD) was prepared by melting, solvent evaporation and kneading method using different ratios of drug and polymers (PEG-4000, Eudragit E-100, PVP K-30, Poloxamer-407, and Eudragit L-100). Phase solubility study revealed highest solubility in PVP K-30 at 1:2 ratios. The solid state characterizations of selected solid dispersion formulation (SD-15) were performed by infrared spectroscopy, differential scanning calorimeter, X-ray diffraction study and scanning electron microscopy. *In vitro* dissolution was carried out in phosphate buffer (pH 7.4) at 50 rpm in 900 ml of volume. The *in vivo* pharmacokinetic study of selected formulation (SD-15) was carried out in male Wistar rats using non-compartment analysis by linear trapezoidal method after a single oral dose of 10 mg/kg of EM. **Results:** The solid state characterization revealed no such drug-polymer interactions and rapid transformation of crystalline drug in an amorphous state, which amplifies the aqueous solubility and hence the dissolution rate. The *in vitro* dissolution study of the dispersions prepared by PVP K-30 (1:2) was found to be 95.5% after 1 hr. *In vivo* pharmacokinetic study in Wistar rats showed significant improvement in oral bioavailability of EM in SD-15 with the 2.4 fold increments than the pure drug. **Conclusion:** The solid dispersion prepared using PVP K-30 by kneading method showed improved dissolution and bioavailability. Therefore, solid dispersion formulation can be sorted as a promising approach for improving the dissolution and bioavailability of Eprosartan mesylate.

Key words: Eprosartan mesylate, Solid dispersion, Dissolution, Bioavailability, Characterization.

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INTRODUCTION

Eprosartan mesylate (EM), chemically *(E)*-4-({2-Butyl-5-2-carboxy-2-(thiophen-2-ylmethyl) eth-1-en-1-yl-1*H*-imidazol-1-yl} methyl) benzoic acid is an anti-hypertensive drug which prevents the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in vascular smooth muscle.[1] EM belongs to the class of BCS-II that demonstrate incomplete absorption from the gastrointestinal tract after oral administration and exhibit biological half life of 5-9 hr.[2,3] EM exhibits pH dependent aqueous solubility and lipophilicity which may result in variable absorption as the compound passes through the gastrointestinal tract.[4] Due to extensive hepatic first pass metabolism in the liver and very low solubility, the resultant bioavailability lies about 13%.[5] Therefore, a high dose of 800 mg is often prescribed

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for the management of hypertension and other cardiac complications, which often precipitates adverse or side-effects. EM bounds extensively with plasma proteins (98%) and having a mean terminal elimination half-life of 20 hr at 600 mg oral dose.[6] EM undergoes little metabolism by oxidative and hydrolytic processes and about 90% of unchanged drug gets eliminated in feces. The roles of CYP_{450} isoenzyme forms in drug metabolic processes are quite limited. The metabolized products are very minute and are generally inactive.[7]

Poorly water-soluble drugs involve many difficulties in the development of pharmaceutical dosage forms for oral delivery systems due to their low bioavailability.[8] During the past few years, there has been a great pace in using solubility enhancement techniques for the improvement of the dissolution rate and subsequently the bioavailability of poorly water soluble drugs. Several techniques like nanomaterialization,[9] salt formation,[10] hydrotropy,[11] liposome formation,[12] liquisolid compaction,[13] solid dispersion,[14] SMEDDS,[15] and many other significant techniques have been reported for improving bioavailability of poorly water soluble drugs of class BCS-II and BCS-IV.

Solid dispersion (SD) is one of the most promising strategies to improve the dissolution properties and bioavailability of poorly water-soluble drugs where drug materials are dispersed in an inert carrier. [16] The drug dispersed in polymeric carriers may achieve the highest levels of particle size reduction, surface area enhancement and may exist in amorphous form in polymeric carriers, which results in improved solubilities and dissolution rates as compared with crystalline material.[17, 18] In these SDs, no energy is required to break up the crystal lattice of a drug during the dissolution process which produced faster release and higher bioavailability than conventional formulations of the same drugs owe to their small particle size and better wettability of the drug.[19]

The objective of the present study was; (1) to improve the solubility of poorly soluble EM using SD method employing various polymers (PEG-4000, Eudragit E-100, PVP K-30, Poloxamer-407, and Eudragit L-100); (2) to perform solid state characterization of selected EM SD using various approaches like IR, DSC, XRD, and SEM; and (3) to carry out a pharmacokinetic study of the optimized SD formulation of EM.

MATERIALS AND METHODS

Materials

EM was obtained as a generous gift from Mylan Laboratories Ltd., Nashik, India. PEG-4000, Eudragit E-100, PVP K-30, Poloxamer-407, and Eudragit L-100 were obtained from Colorcon Asia Pvt. Ltd., Mumbai, India, and Himedia Ltd., India. HPLC grade acetonitrile and orthophosphoric acid were purchased from Merck Chemicals Ltd., Mumbai, India. Double distilled water was used and was suitably filtered through 0.45 μm filter. Miscellaneous ingredients used in the study were of analytical/pharmaceutical grade.

Methods

Drug content estimation

The SDs equivalent to 10 mg of EM were accurately measured and dissolved in 10 mL of phosphate buffer (pH 6.8 and 7.4). The absorbances were recorded at 231 nm using a UV spectrophotometer (UV-1800, Shimadzu, Japan).

Solubility studies

An excess quantity of EM was placed in empty reaction tubes (Hi-media, India) containing 2 ml of phosphate buffer (6.8 and 7.4). The tubes were sonicated (Transonic Digital S, USA) for 10 minutes at 25°C and the reactant mixture was stirred vigorously using a vortex mixer (V-Mixer Scientific, India) for 5 min to facilitate solubilisation of EM in solvent. The reactant mixture was further agitated continuously on a rotary shaker cum incubator (MVTEX, India) at 40°C for 24 hr. After reaching equilibrium, the undissolved EM content in solvent was separated by centrifuging at 10,000 rpm for 5 min and clear supernatants obtained were filtered, suitably diluted and analyzed spectrophotometrically at 231 nm.

Phase solubility study

The phase solubility studies were carried out according to the method reported by Higuchi and Connors.[20] An excess amount of EM was added to the screw capped vials containing 20 ml of an aqueous solution of hydrophilic polymers (PEG-4000, Eudragit E-100, PVP K-30, Poloxamer-407, and Eudragit L-100) at various concentrations (5-100 mM) placed in an orbital shaking incubator and agitated for 24 hr at 37°C. After reaching the equilibrium, the supernatant solutions were filtered suitably by Whatman filter paper (No. 41) and after appropriate dilution; solutions were analyzed by UV spectroscopy at 231 nm.

Preparation of solid dispersions (SDs)

SD is one of the most commonly used techniques to improve the solubility of water insoluble drugs which in turn improves the bioavailability.[21] EM is practically insoluble moiety belonging to the BCS-II class. Therefore,

SDs of EM were prepared by hot melt method, solvent evaporation method and kneading method. In hot melt method, the insoluble drug is dispersed into a molten carrier and cooled immediately. In solvent evaporation method, both drug and the carrier were dissolved in a common volatile solvent, and the solvent was evaporated to get SDs. In the kneading method, both insoluble drug and carrier are kneaded and solid damp mass is formed which is further dessicated to obtain SDs.

Melting method

The melting process was performed as per the method described by Yu *et al*.[22] The carriers; PEG- 4000 and Poloxamer-407 were taken separately in different ratios (1:1, 1:1.5, 1:2) and heated at 50-55°C using a hot plate. The required amount of EM was added in portions to the molten mass of PEG-4000 and Poloxamer-407 separately with continuous stirring using a magnetic stirrer to get the solid mass. The resulting SDs were subsequently desiccated under vacuum for 24 h. The dried mass, then pulverized and passed through sieve No. 80 and were stored in tightly closed container until further study.

Solvent evaporation method

The solvent evaporation process was performed as per the method described by Sethia and Squillante.[23] The drug and carriers; Eudragit E-100 and Eudragit L-100 were taken separately in different ratios (1:1, 1:1.5, 1:2) and transferred in a beaker containing appropriate amounts of ethanol (solvent). Subsequently, the solvent was removed by evaporation on magnetic stirrer with hot plate at temperature 40°C for 1 hr to get SD mass. The resultant dispersions were pulverized in a mortar and passed through sieve No.80 and desiccated under vacuum for 24 hr and finally stored in tightly closed containers.

Kneading method

The kneading process was performed as per the method described by Maulvi *et al*.[24] The drug and carriers (Eudragit E-100 and Eudragit L-100) were taken in different ratios (1:1, 1:1.5, 1:2) and mixed well with sufficient quantity of ethanol to produce a solid damped mass. The solid masses were kneaded thoroughly for 30 min in glass mortar and desiccated under vacuum for 24 hr. Finally, the SDs were pulverized and passed through sieve No. 80 and stored in tightly closed containers.

Pharmacokinetic study

The pharmacokinetic study of optimized SD was performed and compared with the standard EM. Wistar male rats aged 5-6 weeks, average weight 225-255 gm, housed in clean polypropylene cages with free access to water and standard rodent pellets were used for the study after approval by the Departmental Animal House Facility with permission of the Department Ethical Committee and CPCSEA (KNCOP/R&D/AN-PROT/14-15/02) of Kamla Nehru College of Pharmacy. The pharmacokinetic study for EM SDs was performed as per the method described by Dangre and Dhole.[25] The rats were fasted overnight before the dosing with free access to water. The rats were divided into two treatment groups (n=3) and each were treated with standard EM and selected SD. EM SD prepared from PVP K-30 (1:2) was suspended in 0.5% sodium carboxyl methyl cellulose and administered to rats by oral gavage (10 mg/kg). After oral administration, blood samples of 0.5 ml were collected from the retro-orbital plexus at 0.5, 1, 2, 4, 6, 8, 12, and 24 hr. Plasma was separated from each blood sample by centrifugation at 10,000 rpm for 10 min and stored at -20°C until analysis. Aliquots of 100 µL samples were processed by single step protein precipitation method where 100 µL of the drug spiked plasma sample was pipetted into a heparinized centrifuge tube. The plasma was then deproteinized, to free the bound EM, using acetonitrile with a ratio of 1:3 (v/v) acetonitrile: plasma. The plasma: acetonitrile mixtures were vortex mixed for 3 min and then centrifuged at 5,000 rpm for 5 min. The clear supernatant samples were collected and injected into the HPLC system to analyze the EM concentrations. The HPLC system comprised of Shimadzu LC-2010 CHT (Japan) model with SPD 20-AD UV-visible detector. The chromatographic separation was performed on Phenomenox C_{18} (250 x 4.6 mm i.d., particle size 5 µm) column. The mobile phase consisting of acetonitrile: water (45:55% v/v) with pH 3.4 adjusted with *orthophosphoric* acid (85% v/v), at a flow rate of 1 mL/ min was selected. The pharmacokinetic parameters were calculated from measured EM plasma concentrations versus time profile using a non-compartment model with a linear trapezoidal method by PK Solver 2.0 software.

Characterization of solid dispersions

Solid state characterization was performed for drug, polymers and selected SDs.

Infrared spectral analysis

IR absorption spectrum (FTIR spectrophotometer, GX-FT-IR, Perkin Elmer, USA) of EM (pure drug) and selected formulations of SDs were recorded by potassium bromide dispersion technique in the range of 4000–400 cm^{-1}. The compounds were scanned at a resolution of 0.15 cm^{-1} and scan speed was 20 scan/s.

Differential scanning calorimeter analysis

The physical state of EM and selected formulation of SDs was characterized by differential scanning calorimeter (DSC) thermogram analysis. The DSC patterns were recorded on a Pyris Diamond TG/DTA Perkin Elmer. Each sample was heated in a platinum crucible along with alpha alumina powder as a reference at a scanning rate of 10°C/min in an atmosphere of nitrogen (150 mL/min) using the range of 30-300°C. The temperature calibrations were performed periodically using indium as a standard.

X-ray Diffraction analysis

The physical state of EM and SDs formulations was characterized by X-ray powder scattering (XRD) measurements using X-ray diffractometer (ULTIMA-III, RIGAKU, Japan). The measurements were performed at room temperature using monochromatic CuK- radiation (Cu target, slit 10 mm) at 40 KV over a range of 7 to 80 with a continuous scanning speed of 4/min. The analyzed sample was compactly packed in the cavity of an aluminium sample holder using a glass slide.

Scanning electron microscopy analysis

The external morphology of the EM and selected formulation of SDs was studied by scanning electron microscopy (SEM). The samples for SEM were prepared by slightly sprinkling powder on a double adhesive tape stuck to an aluminium stub. Afterwards, the stub containing the coated samples was placed in the scanning electron microscope (SEM) chamber. The samples were then randomly scanned and photomicrographs were taken at the acceleration voltage of 10 kV and the result of SEM was reported.

In vitro dissolution study

The *in vitro* dissolution study of pure drug and SDs were performed using dissolution test apparatus USP 33 (Type II) apparatus in 900 ml of dissolution medium containing sodium lauryl sulfate (0.5%) in simulated gastric fluid without enzyme, pH 7.4 maintained at 37 ± 0.5°C at a speed of 50 rpm. The pure drug and SDs equivalent to 400 mg of EM were separately placed in dissolution medium. From each vessel at specific time interval, 1 ml of sample was withdrawn, filtered through Whatman filter paper (No.41), diluted and analyzed spectrophotometrically (Shimadzu UV-1800, Kyoto, Japan) at 231 nm. An equal volume of fresh medium which was prewarmed at 37 ± 0.5°C, replaced in the dissolution medium after each sampling to maintain the constant volume throughout the test. The release studies were conducted in triplicate. The data were studied using PCP-Disso v2.08 software.

RESULT AND DISCUSSION

Drug content

The drug content was observed in the range of 86.03-93.59% in phosphate buffer at pH 6.8, while the drug content was observed in the range of 94.19-99.46% in phosphate buffer at pH 7.4 using kneading method (Table 1). PVP K-30 displayed the highest; 99.46 ± 0.41% drug content in 1:2 ratio at pH 7.4, compared to other SDs prepared by fusion method and solvent evaporation method.

Solubility studies

The solubility studies have revealed that higher saturation solubility (mg/mL) at pH 7.4 than at pH 6.8. The saturation solubility was found to be in the range 81.2-153.3 mg/mL at pH 7.4. The kneading method shows better saturation solubility of SDs prepared by using carrier PVP K-30 in the ratio of 1:2 in pH 7.4 as compared to fusion method and solvent evaporation method. The increase in the saturation solubility of drug can be explained by improved dissolution of SDs.

Phase solubility study

The plot of EM solubility in PVP K-30 polymer indicated that the solubility gets increased with increasing concentration of the carrier (Figure 1). The plot between EM and PVP K-30 aqueous solution showed the highest phase solubilization as compared to other polymeric solutions.

Infrared spectral analysis

The FTIR spectrum of drug and SDs are shown in Figure 2. The spectrum of EM (Figure 2a) showed characteristic peaks at 3103 (OH carboxylic), 2873 (alkane stretch), 1710 (C=O stretching), 1647 (C=N), 1614 (C=C), and 1311 (C-N), respectively. The spectrum of SD of EM (Figure 2b) exhibited analogous results. The observed prominent peaks are 3103 (OH carboxylic), 1716 (C=O stretching), 2864 (alkane stretch), 1683 (C=N), 1616 (C=C), and 1313 (C-N), respectively, which are quite similar to the spectrum of EM. This concluded that there were no such drug-polymer interactions in the SDs.

Differential scanning calorimeter analysis

The DSC thermograms of pure drug (EM) and SD are described in (Figure 3). The drug exhibited sharp endothermic peak at 250.66°C with peak onset at 246.18°C (Figure 3a), which corresponds to its melting point, thereby confirming the crystalline nature. In contrast, the SD of drug: PVP K-30 in 1:2 ratio demonstrated broad endothermic peak (Figure 3b) over the entire scanning

Table 1: Drug content and saturation solubility of solid dispersions prepared by various methods

Batch Code	Solid dispersion system	Method of preparation	Ratio of drug: carrier	Drug content (%) Saturation solubility			
				pH 6.8	pH 7.4	pH 6.8	pH 7.4
SD-1	Eprosartan : Poloxamer 407	Melting	1:1	86.10 ± 0.10	94.19 ± 0.17	64.19 ± 0.20	81.22 ± 0.23
SD-2	Eprosartan : Poloxamer 407	Melting	1:1.5	88.41 ± 0.51	94.28 ± 0.25	68.28 ± 0.25	93.04 ± 0.08
SD-3	Eprosartan : Poloxamer 407	Melting	1:2	88.87 ± 0.24	95.33 ± 0.49	74.35 ± 0.32	94.18 ± 0.16
SD-4	Eprosartan : PEG 4000	Melting	1:1	86.03 ± 0.15	95.61 ± 0.55	59.23 ± 0.23	92.02 ± 0.02
SD-5	Eprosartan : PEG 4000	Melting	1:1.5	86.10 ± 0.10	96.07 ± 0.07	60.39 ± 0.35	96.31 ± 0.28
SD-6	Eprosartan : PEG 4000	Melting	1:2	89.03 ± 0.15	96.24 ± 0.55	63.23 ± 0.09	102.4 ± 0.45
SD-7	Eprosartan : Eudragit E 100	SE	1:1	84.01 ± 0.10	94.51 ± 0.03	58.29 ± 0.27	103.3 ± 0.40
SD-8	Eprosartan : Eudragit E 100	SE	1:1.5	85.83 ± 0.55	97.16 ± 0.15	66.37 ± 0.02	112.3 ± 0.20
SD-9	Eprosartan : Eudragit E 100	SE	1:2	86.28 ± 0.30	97.46 ± 0.04	78.30 ± 0.54	113.1 ± 0.25
SD-10	Eprosartan : Eudragit L 100	SE	1:1	86.31 ± 0.33	96.53 ± 0.40	72.34 ± 0.31	83.76 ± 0.09
SD-11	Eprosartan : Eudragit L 100	SE	1:1.5	87.34 ± 0.54	97.32 ± 0.68	73.01 ± 0.01	97.48 ± 0.42
SD-12	Eprosartan : Eudragit L 100	SE	1:2	87.95 ± 1.56	98.51 ± 0.54	74.02 ± 0.05	101.6 ± 0.49
SD-13	Eprosartan : PVP K-30	Kneading	1:1	90.15 ± 0.21	98.33 ± 0.33	79.22 ± 0.20	99.37 ± 0.32
SD-14	Eprosartan : PVP K-30	Kneading	1:1.5	93.59 ± 0.52	99.10 ± 0.10	77.53 ± 0.49	129.0 ± 0.05
SD-15	Eprosartan : PVP K-30	Kneading	1:2	92.10 ± 0.53	99.46 ± 0.41	75.45 ± 0.50	153.3 ± 0.28
SD-16	Eprosartan : Eudragit L 100	Kneading	1:1	89.62 ± 1.67	95.06 ± 0.13	63.20 ± 0.18	93.42 ± 0.13
SD-17	Eprosartan : Eudragit L 100	Kneading	1:1.5	90.96 ± 0.30	96.49 ± 0.44	77.48 ± 0.45	95.68 ± 0.05
SD-18	Eprosartan : Eudragit L 100	Kneading	1:2	93.08 ± 0.11	98.20 ± 0.27	77.70 ± 1.88	122.5 ± 0.53
D	Pure drug	-	-	-	-	15.33 ± 0.29	48.53 ± 0.47

SE, solvent evaporation

Table 2: Pharmacokinetic parameters for pure drug suspension and solid dispersion (SD-15)

Pharmacokinetic Parameters	Drug in suspension	SD-15
AUC_{0-t} (ng/mL* h)	2679.4 ± 421.2	6627.6 ± 256.4
$AUC_{0-\infty}$ (ng/mL* h)	3637.7 ± 354.1	8127.6 ± 367.6
C_{max} (ng/mL)	924 ± 24.3	2147.34 ± 27.3
T_{max} (h)	2.0 ± 0.0	1.5 ± 0.0
$t_{1/2}$ (h)	6.49 ± 0.4	7.6 ± 0.8
Relative bioavailability	-	2.4

SD-15, solid dispersion prepared with PVP K-30, AUC_{0-t} – area under the concentration time profile curve until last observation, $AUC_{0-\infty}$ -- area under the concentration time profile curve extrapolated to infinity, C_{max} – peak of maximum concentration, T_{max} – time of peak concentration, $t_{1/2}$ – elimination half life.

range of 30°C-300°C, suggesting rapid transformation into amorphous nature. Thus, it may be concluded that no such characteristic pure drug peak indicated the change in melting behaviour of drug and inhibition of crystallization since amorphous state is considered as a state of high disorder, the solid particles present remain in highly dissolved state. However, Figure 3b shows an endothermic peak whose onset temperature approximately coincides with that for the endothermic peak of (Figure 3a). The probable reason may be that in solid dispersions, the endothermic peak gets broadened and shifted toward low temperature which may be due to the higher polymeric concentrations and distribution of drug in the polymer layer causing the entire molten drug to be miscible in the polymer core.[26]

Powder X-ray Diffraction analysis

Powder-X-ray diffraction (P-XRD) study provides information of the crystalline nature of drugs and reveals the possible arrangement of atoms inside the crystal lattice. The appearance of several intense crystalline peaks reflects the existence of EM in crystalline

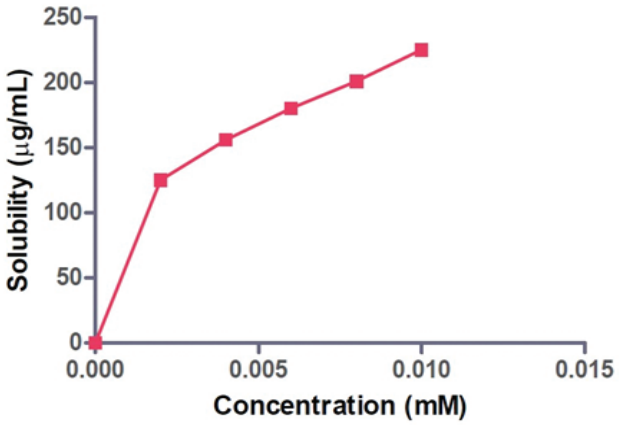

Figure 1: Phase solubility plot of eprosartan mesylate in PVP K-30.

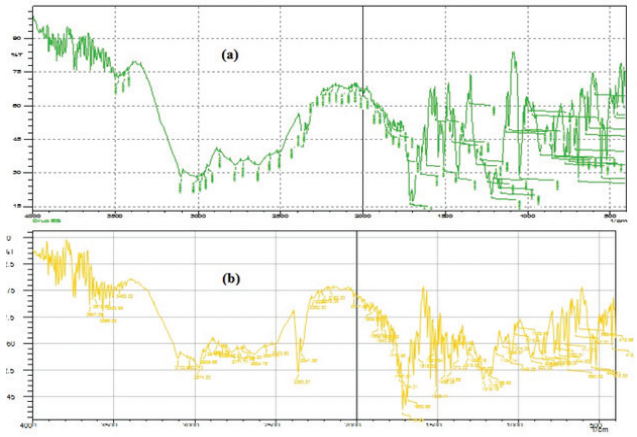

Figure 2: Fourier transfer infrared spectra (FTIR) of eprosartan mesylate (pure drug) and solid dispersion (SD-15).

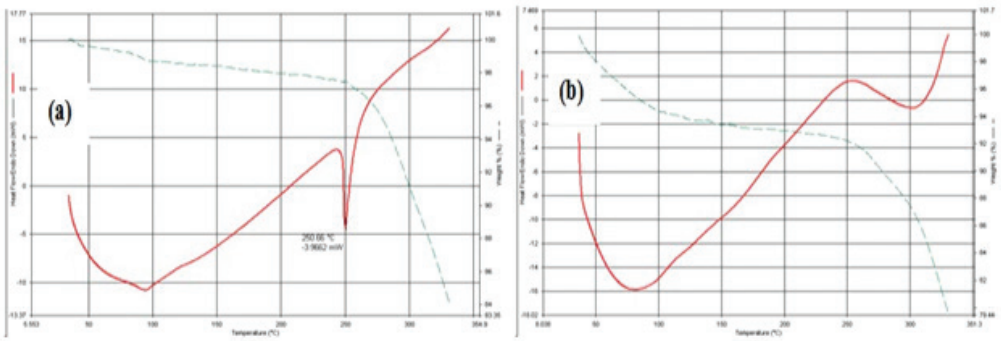

Figure 3: Differential scanning calorimetric thermogram: (A) Eprosartan mesylate (pure drug), (B) Solid dispersion formulation (SD-15).

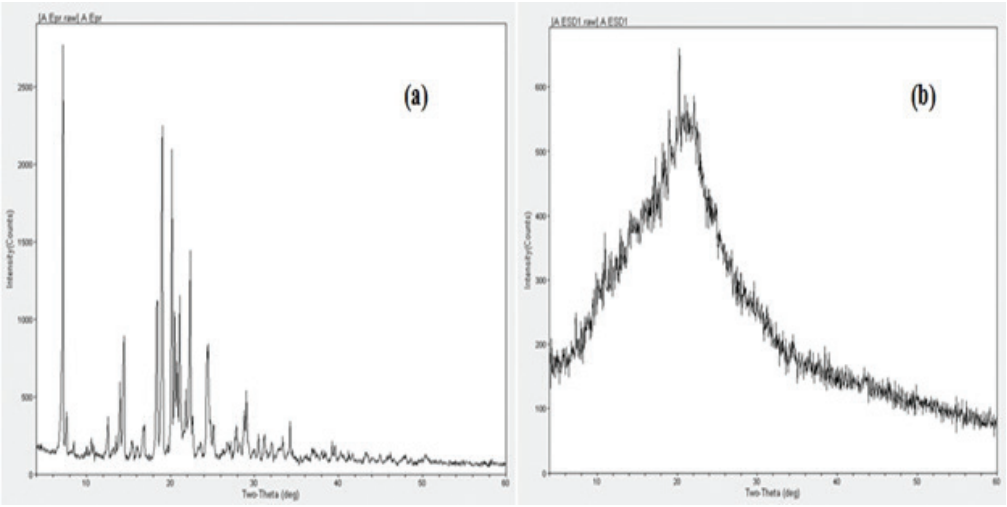

Figure 4: Powder X-ray diffraction spectra of (A) Pure drug of EM, (B) Solid dispersion formulation (SD-15).

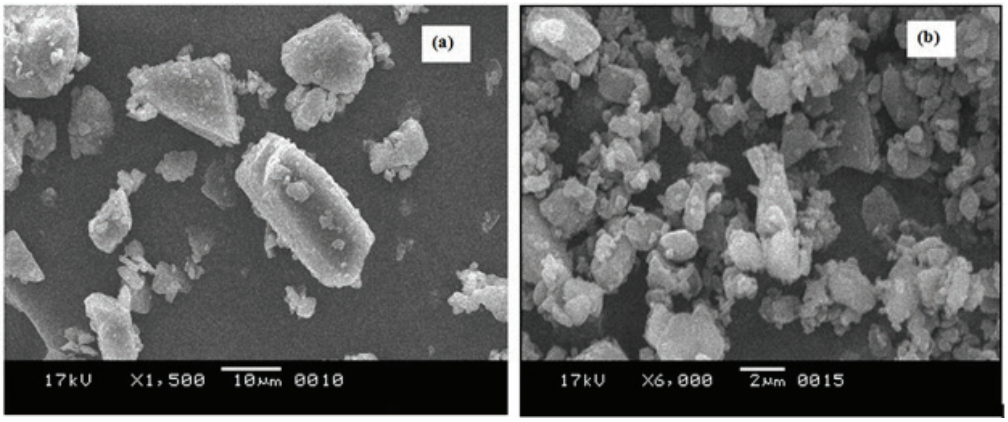

Figure 5: Scanning electron micrograph; (a) Eprosartan mesylate (pure drug); (b) Solid dispersion formulation (SD-15).

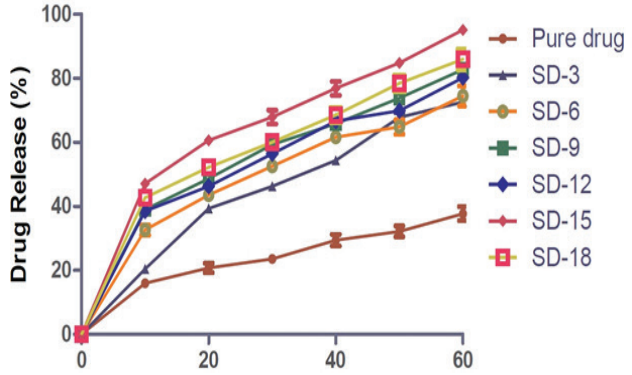

Figure 6: *In vitro* dissolution profile of pure drug of eprosartan mesylate and solid dispersion formulation prepared with 1:2 (drug: polymer ratio) (Mean ± SD; n=3).

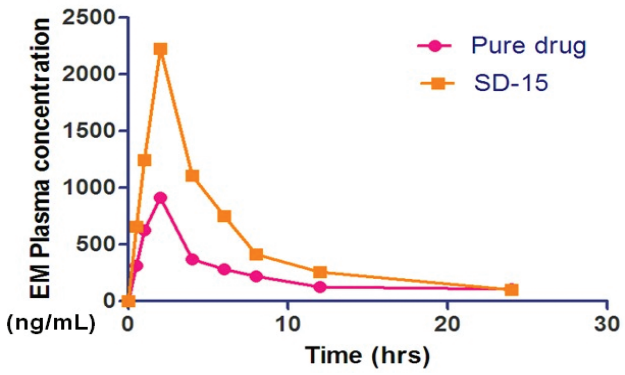

Figure 7: The mean plasma concentration vs. time profile of pure drug and selected solid dispersion formulation (SD-15) in rats after oral administration (Mean ± SD, n=3).

state (Figure 4a). However, an analysis of PXRD pattern of SDs (Figure 4b) depicted no such significant peaks which stalwartly confirmed the molecularly dispersed state of EM in the formulation and effective solubilisation of the drug. In formation of SDs, the drug experienced swift renovation from crystalline state to its amorphous form, which is having high internal energy, thereby resulting in prompt dissolution of drug materials as compared to its crystalline forms.

Scanning electron microscopy analysis

The surface morphology of pure drug (EM) and SD were investigated using scanning electron microscope (SEM) and their micrographs are shown. Pure EM appeared as rod shaped crystals having a very rough surface (Figure 5a). In contrast, the photomicrograph of surface SD (Figure 5b) indicated the uniform surfaces, smooth particle with aggregated spherical particles and deep crevices. This suggested that entire drug was distributed uniformly in the carrier mass and represented well separated particles.

In vitro dissolution

The *in vitro* drug release profile of SDs were studied and compared with the pure drug of EM (Figure 6). In all the SDs prepared by different methods, the SDs with 1:2 ratios (drug: polymer) exhibited higher drug content as well as maximum saturation solubility of the drug. Therefore, the SDs prepared with 1:2 ratios were employed for drug release study. Among all the batches, the dispersion prepared by kneading, using PVP K-30 (SD-15) showed a better drug release profile. The improvement in dissolution rate was also observed in all the formulations of SDs prepared by solvent evaporation and melting method using Polaxamer-407, PEG-4000, Eudragit L100, and Eudragit E 100. The results suggest significant improvement in dissolution of SDs prepared by kneading method using PVP K-30 (95.5%). The SDs prepared with higher ratios of polymer could offer more available space for surrounding of hydrophobic drug particle resulted in rapid hydration of drug molecules and consequently better wettability

and enhancement in the dissolution. Moreover, the transformation of the crystalline nature of pure EM into the amorphous form as affirmed by the DSC and PXRD results facilitates higher drug release rate over the pure drug. As shown in (Figure 6), the SDs prepared by kneading method using PVP K-30 was found to be superior and simple over the other conventional methods of SDs.

The reason for the superior dissolution by kneading method may be attributed due to better reduction of particle size and promotion of amorphous nature to the drug resulting in improved release and enhanced exposed surface area promoting higher dissolution. In the binary state, drug particles lie in contact with the polymeric phase. When the drug and polymer comes in contact with aqueous phase, the polymeric units get hydrated into its solution state, which consequently promote solubilization of the drug causing release of drug into the media. At low concentration of polymers, monomolecular micelles are formed which endorse dissolution of drug in media, as the concentration increases, the micelles aggregate to form multimolecular micelles which solubilizes the drug to still high extent.[27] The ratio of the free drug concentration to the crystalline equilibrium solubility, can also be used to define the supersaturation. The inhibition of crystallization during dissolution enables supersaturated solution to be generated under non-sink dissolution conditions. A solution with a free drug concentration below the crystalline solubility has a supersaturation <1 and will not crystallize. In contrast, a solution with a free drug concentration greater than the crystalline solubility has a supersaturation >1, and a thermodynamic driving force for crystallization.[28] The SDs exhibited supersaturated solution owing to inhibition of crystallization during dissolution with free drug concentration below the crystalline solubility. Both theoretical and practical supersaturation value was found to be <1.

Pharmacokinetic study

The *in vivo* pharmacokinetic parameters of SD-15 and standard EM were studied in Wistar rats. The measured mean EM plasma concentrations versus time after single oral administration in male Wistar rats using 0.5% oral suspension are depicted in (Figure 7). The pharmacokinetic parameters calculated from the non-compartment model using linear trapezoidal method are described in (Table 2). Relative bioavailability was calculated by using the following formula:

$$\text{Relative bioavailability (\%)} = AUC_{test} / AUC_{reference} \times Dose_{reference} / Dose_{test}$$

The pharmacokinetic parameters of EM, obtained from non-compartmental analysis using a linear trapezoidal method after a single oral dose of 10 mg/kg of EM to Wistar rats. The $t_{1/2}$, T_{max} and C_{max} of the drug was found to be about 6.49 hr, 2 hr, and 924 ng/mL respectively along with AUC_{0-t} of 2679.4 ng/mL*h. In contrast, the SD-15 demonstrated higher C_{max} and AUC_{0-t} as compared to standard drug suspension (C_{max} = 2147.34 ng/mL, AUC_{0-t} = 6627.6 ng/mL*h). Conversely, the T_{max} of the SD-15 was delayed as compared to the standard EM (T_{max} = 1.5 hr). The relative bioavailability of SD-15 formulation was found to be about 2.4 folds higher, which may be due to conversion of drug into its amorphous form in SDs which is having high internal energy that promotes quick dissolution and hence higher bioavailability was observed (Figure 7).

CONCLUSION

The current study highlighted a simple method for the fabrication of SDs. The study indicated that the SDs of eprosartan mesylate prepared using PEG-4000, Eudragit E-100, PVP K-30, Poloxamer-407, and Eudragit L-100 have successfully enhanced the solubility of drug which in turn improved the dissolution profile. The nature, type, process, and the amount of the carrier used have played an imperative role in the improvement of dissolution rate. The rapid transformation of crystalline drug to amorphous state and prompt reduction in onset of action by amplifying the aqueous solubility and dissolution rate leads to better bioavailability profile. The dissolution rate of the SDs prepared by PVP K-30 (1:2) with kneading method was observed to be higher than the others prepared by PEG 4000 (1:2), Eudragit L (1:2) and Poloxamer 407 (1:2). The DSC thermogram also suggests that in the kneading process, the drug crystals get dispersed in the carrier and no molecular interactions were observed, suggesting no interaction between the components of two systems. This study opened new doors for therapeutic perspective of EM in coming future.

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CONFLICT OF INTEREST

Authors have no conflict of interest with the content of this article.

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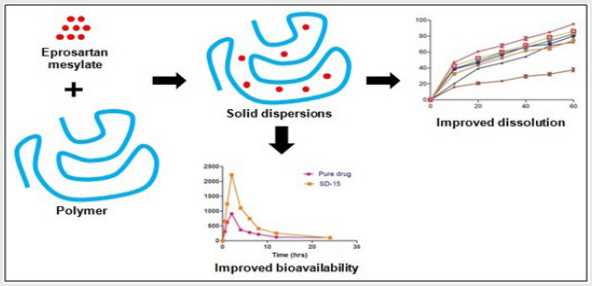
PICTORIAL ABSTRACT



SUMMARY

- EM's bioavailability is enhanced by formation of solid dispersions.
- Polymers (PEG-4000, Eudragit E-100, PVP K-30, Poloxamer-407, and Eudragit L-100) are used for formulation.
- Characterization was done by infrared spectroscopy, differential scanning calorimeter, X-ray diffraction study and scanning electron microscopy.
- The *in vivo* pharmacokinetic study of SD-15 is performed using non-compartment analysis by linear trapezoidal method.