



ISSN No: 0975-7384
CODEN(USA): JCPRC5

J. Chem. Pharm. Res., 2011, 3(6):536-543

Lansoprazole solid dispersion using a novel amphiphilic polymer Soluplus[®]

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ABSTRACT

The aim of the present study was to prepare solid dispersion (SD) of Lansoprazole (LSP) to improve its saturation solubility and dissolution. SDs were prepared with a hydrophilic polymer PEG 4000 and a novel amphiphilic polymer Soluplus[®]. SD prepared using Soluplus[®] by solvent evaporation method gave highest saturation solubility. The prepared SD was further characterized by Fourier Transform Infrared Spectroscopy (FTIR), Powder X-Ray Diffraction (XRD), Differential Scanning Colorimetry (DSC), Scanning Electron Microscopy (SEM) and in vitro drug dissolution. FTIR suggested formation of intermolecular hydrogen bonding between LSP and Soluplus[®]. DSC and XRD studies revealed partial amorphization when compared to pure LSP. The results of in vitro dissolution in distilled water indicated a remarkable improvement in dissolution from the SD with 100% release in 20 mins when compared with the pure LSP (40% release in 120 mins).

Key Words : Lansoprazole, Solid dispersion, Solubility improvement, Soluplus[®].

INTRODUCTION

Formulation of poorly water soluble drug is a major challenge for the formulation experts. Various techniques can be used to increase the solubility of these drugs such as use of surfactants, formation of inclusion complex and preparation of solid dispersion (SD). Increase in solubility can improve dissolution and in turn the oral bioavailability as well as the therapeutic efficacy and patient compliance [1]. SD system may be crystalline or amorphous solid solution, a dispersion of crystalline or amorphous drug particles in crystalline or amorphous carrier matrix, or combination of solution and dispersion of solids. Different types of SD systems and their drug release mechanisms have been reviewed in depth [2]. The methods to prepare SD include fusion

method, solvent evaporation, spray drying, hot melt extrusion, solvent deposition technique, supercritical fluid method and solvent wetting method [3, 4]. Most of the methods cite use of hydrophilic carriers such as polyvinylpyrrolidone [5], polyethylene glycols [6], colloidal silicon dioxide [7], and lipids such as gelucire [8]. The solubilization of drug from SD is improved because of size reduction, reduction in crystallinity and increase in surface area as well as wettability and no energy is required to break crystal lattice of drug during solubilization as well as for dissolution process [9].

Lansoprazole (LSP) is used in the treatment of gastric and duodenal ulcerative diseases [10]. It is a BCS class II drug characterized by low solubility and high permeability [11] with bioavailability of 80-91%. Earlier literature suggests that dissolution and oral bioavailability of LSP can be improved by solid preparations comprising surfactants and porous adsorbents [12]. SD of LSP was earlier prepared using PVP by fluid-bed coating technique [13]. However this included use of large amount of surfactants (10% w/v) and polymers to increase the solubility of LSP. Although the performance of such solid dispersions in terms of improved dissolution is laudable, the high amount of the hydrophilic polymers makes the material hygroscopic and sticky thus making the subsequent processing and handling of the material cumbersome.

Thus the present study was undertaken to prepare SD of LSP such that it would result in maximum increase in saturation solubility and dissolution using minimal amount of the carrier. An amphiphilic polymer Soluplus[®] was explored as a carrier for preparation of the SD. Also for comparative purpose SDs were prepared using an established hydrophilic polymer PEG 4000. The prepared SD was characterized by saturation solubility, FTIR, XRD, DSC, SEM and *in vitro* drug dissolution.

EXPERIMENTAL SECTION

Materials

LSP was received as a kind gift sample from Wockhardt Limited (Aurangabad, India). Soluplus[®] was received as gift sample from BASF, India. PEG-4000 was purchased from Loba chemie, Mumbai. Double-distilled water was used throughout the study and all the other chemicals used were of analytical grade.

Method

Preparation of LSP SD

The SD of LSP with PEG 4000 and Soluplus[®] was prepared by solvent evaporation method. Here, a required amount of PEG 4000 and Soluplus[®] was dissolved in methanol to which LSP was added slowly with stirring (drug:polymer 1:1). The solvent was evaporated under reduced pressure at 40°C using a rotary evaporator (Superfit Model-01222) and the residue dried under vacuum for 3 hrs. The mixture was stored overnight in a desiccator. The hardened mixture was powdered in a mortar, sieved through a 100- mesh screen, and stored in a screw-cap vial at room temperature until further use.

Characterization of prepared SDs**Loading Efficiency:**

10 mg of SD product was dissolved in 10 ml methanol and further dilutions were done in methanol as required. Analysis was carried out using UV spectrometer (Jasco UV visible spectrophotometer 1601, Japan) at 283nm.

Solubility Studies

An excess amount of LSP and SDs were added separately in 10ml distilled water and shaken using mechanical shaker at 25°C for 48hrs. After reaching equilibrium, samples were centrifuged at 10,000 rpm for 10 minutes; aliquots were withdrawn, filtered through membrane filter (0.45µm, Whatman, USA) for further quantification of drug using UV spectrometer (Jasco UV visible spectrophotometer 1601, Japan) at 283nm.

Fourier Transform Infra-Red Spectroscopy (FTIR)

LSP and prepared SDs were analyzed by FTIR (Jasco FT/IR- 4100, V-5300, Japan) by mixing with KBr in mortar and pestle in the ratio of 1:10. The resulting mixture was then analyzed by FTIR from wavenumber range 400 to 4000 cm⁻¹ and characteristic peaks were recorded.

Differential Scanning Calorimetry (DSC)

DSC measurements were performed using METTLER Toledo Star 821e (Switzerland). The samples of pure drug and prepared SDs (5-10mg) were hermetically sealed in aluminum pans and heated at a constant rate of 20 °C/min over a temperature range of 25–200°C. An inert atmosphere was maintained by purging with nitrogen gas at a flow rate of 20 ml/min.

X-Ray Powder Diffractometry (XRPD)

The powder XRD patterns were recorded using an X-ray Brucker AXS diffractometer (Model: D8 Advance, USA), with Copper as anode material and crystal graphite mono-chromator operated at a voltage of 40 kV and a current of 30 mA (step size 0.05, counting time 1s/step). The samples were analyzed in the 2θ angle range of 2 to 30° at scan rate of 1°/min. The range and the chart speed were 5 x 10³ CPS and 10 mm/2θ, respectively.

Scanning Electron Microscopy (SEM)

Surface characteristics of pure drug and prepared SDs were observed using scanning electron microscope (JEOL, JSM- 6360 Tokyo, Japan). Samples were placed on a carbon specimen holder, and then coated with carbon in an auto fine coater (JEOL JFC 1600).

In Vitro Dissolution Study

In vitro dissolution study of LSP and solid dispersion equivalent to 30mg of pure LSP was performed at 37±0.5 °C, using six-station USP type II apparatus (LABINDIA, DS8000, India) rotating at 75 rpm using distilled water as dissolution medium. 5ml aliquot was withdrawn at definite time intervals and replaced with equivalent amount of fresh medium to maintain the sink condition and analyzed using UV spectrophotometer (Jasco V -530, Japan) at 283 nm.

Stability study

The stability of prepared SD was monitored over 3 months at 40 °C/75% RH. Periodically (initially, after 1 month and after 3 months) samples were removed and characterized by DSC

and XRD to monitor changes in the crystallinity. The *in vitro* dissolution studies of the same samples were also carried out.

RESULTS AND DISCUSSION

Preparation of solid dispersion

Solid dispersion method is an effective approach to increase the aqueous solubility of drug by incorporating them into a water soluble polymer matrix. Polyethylene glycols (PEG) are widely used as carriers to prepare solid dispersions. Solvent evaporation method was used to prepare solid dispersion of LSP containing PEG 4000 and novel amphiphilic polymer Soluplus[®] (drug:polymer 1:1) (Soluplus is polyvinyl caprolactum-polyvinyl acetate-poly ethylene glycol graft copolymer).

Characterization of prepared SDs

Drug content

The SD batch containing PEG 4000 in the ratio of 1:1 showed drug content of 77.42% while batch with Soluplus (1:1) revealed drug content of 98.42%. Some loss of drug in SD may be during processing.

Solubility Studies

The solubility of pure drug in distilled water was found to be 0.1365mg/ml. A 2 fold increase in saturation solubility was observed in case of SD prepared by PEG 4000 (0.3259mg/ml). This increase in aqueous solubility may be due to coating of PEG 4000 on drug particles, increased wettability and alteration of surface properties of the drug particle (15, 16). SD prepared using Soluplus[®] resulted in a significant increase in solubility by 11 fold (1.57mg/ml). Soluplus[®] is polyvinyl caprolactum-polyvinyl acetate-polyethylene glycol graft polymer. The amphiphilic nature of Soluplus[®] thus acts as a micellar solubilizer for the drug. Soluplus[®] form large colloidal micelles which entrap the drug molecules and increase the solubility of the drug [17]. Thus with minimal amount of the amphiphilic carrier a remarkable improvement in the solubility of the drug is achieved without compromising the material properties of the product.

Fourier Transform Infra-Red Spectroscopy (FTIR)

FTIR studies were performed to detect the possible molecular interaction between LSP and Soluplus[®] in the solid dispersion system. FTIR spectra of LSP, Soluplus[®] and SD prepared with Soluplus[®] are presented in Fig. 1. The characteristic absorption peaks of LSP appeared at 3276.47, 2984.3 & 2930.31, 1580.38, 1283.39, 1118.51 denoting stretching vibration of -NH, -CH₂, aromatic ring, C-O and ether bond, respectively. Soluplus[®] showed peaks at 3654.44, 2965.98, 1692.23, 1477.21 attributed to O-H stretching, aromatic C-H stretching, C=O stretching, C-O-C stretching. The FTIR spectra of solid dispersion of LSP and Soluplus[®] showed additional band at 3629.37 indicative of intermolecular hydrogen bonding between LSP & Soluplus[®].

Differential Scanning Calorimetry (DSC)

Thermal behavior of pure LSP, Soluplus[®] and LSP SD prepared using Soluplus[®] are depicted in Fig. 2. The pure LSP showed melting endothermic peak at 178.6 °C indicating crystalline nature of LSP, followed by exothermic peak at 181.7°C which may be due to decomposition of LSP.

The DSC thermogram of Soluplus[®] showed a change in the heat capacity at 70°C indicating the glass transition temperature (T_g) of the polymer. The endothermic peak for the drug disappeared in LSP SD thermogram indicating absence of melting endotherm of LSP. This revealed that LSP exist in an amorphous state or as a solid solution in the prepared SD.

X-Ray Diffractometry (XRD)

XRD analysis was performed to confirm the results of FTIR and DSC studies and is presented in Fig. 3. XRD pattern for pure LSP presented several diffraction peaks indicating the crystalline nature of the drug. Peaks for crystallinity were observed at 2θ 2.2°, 2.3°, 4.4°, 4.9°, 5° and 17.5°. The absence of sharp peaks evidenced amorphous nature of Soluplus[®]. The diffractogram of SD prepared by using Soluplus[®] showed decrease in intensity and absence of some major LSP crystalline peaks indicating partial loss of crystalline nature. An amorphous or metastable form will dissolve at the fastest rate because of its higher internal energy and greater molecular motion [18].

Scanning Electron Microscopy (SEM)

Surface morphology of pure LSP and LSP SD prepared using soluplus were studied by SEM (Fig. 4). Pure LSP appeared as fluffy crystalline solid while SD prepared by using Soluplus[®] appeared as a porous mass. This revealed that Soluplus[®] played very important role in controlling the surface morphology of LSP particles.

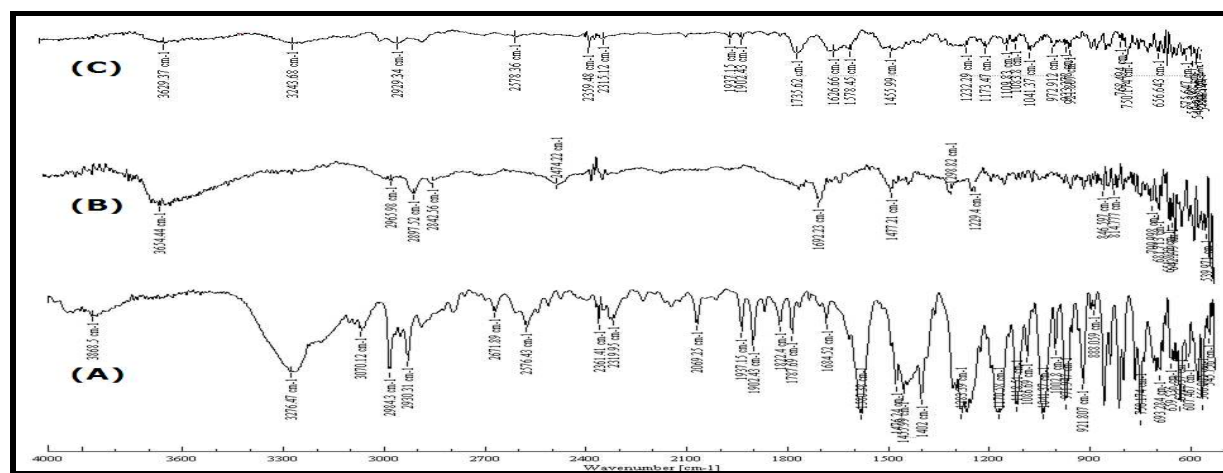


Fig 1. FT-IR spectra of A) LSP, B) Soluplus[®] and C) SD with Soluplus (1:1)

In Vitro Drug dissolution

Dissolution studies in distilled water (Fig.5) revealed 40% release of pure LSP at the end of 120 min. LSP SD (with Soluplus[®] 1:1) released 100% drug in 20 min. Thus the use of Soluplus results in considerable improvement in the dissolution rate of the drug.

Stability study of SD

In the present study, accelerated stability studies were performed at 40 °C/75% RH as per the ICH guidelines. Based on the results of initial characterization, the SD was thought to be more beneficial in comparison to pure LSP and hence was further subjected to accelerated stability

studies. The prepared SD were stable with respect to XRD, DSC and Invitro dissolution for 3 months.

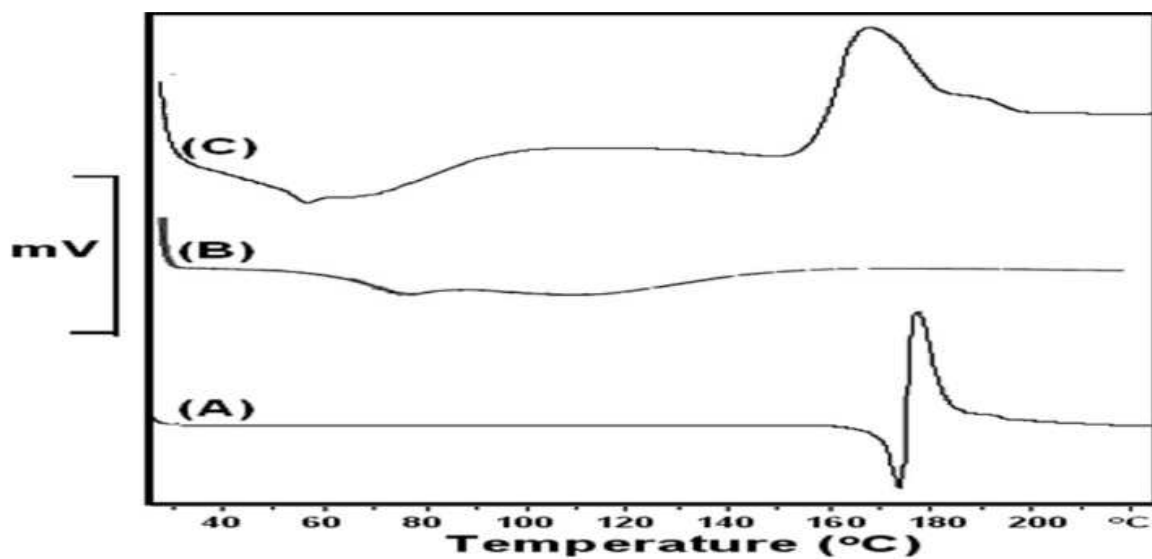


Fig 2. DSC curves of A) LSP, B) Soluplus[®] and C) SD with Soluplus (1:1)

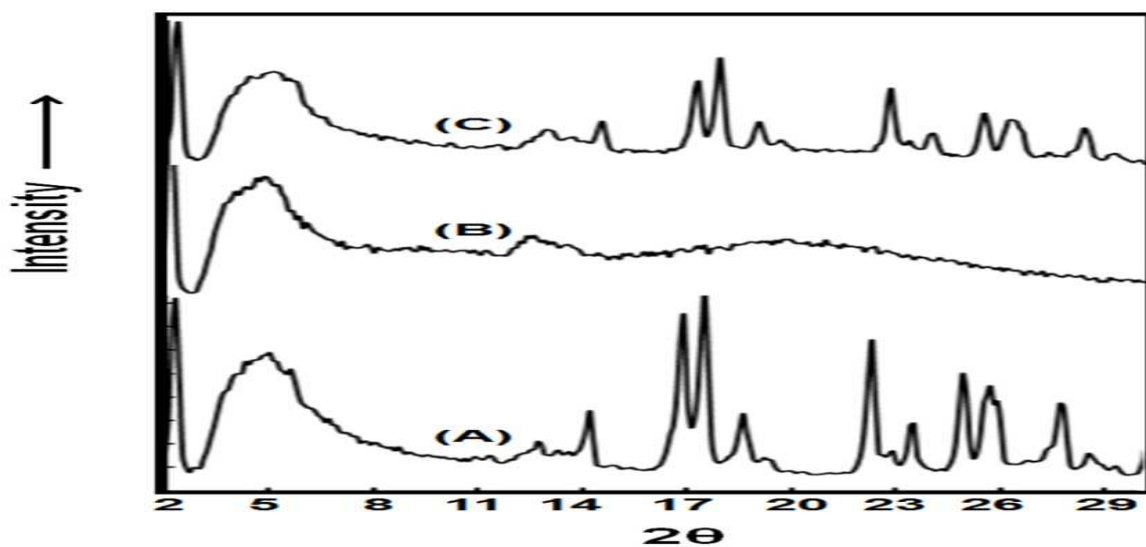


Fig 3. Powder X- ray Diffractograms of A) LSP, B) Soluplus[®] and C) SD with Soluplus (1:1)

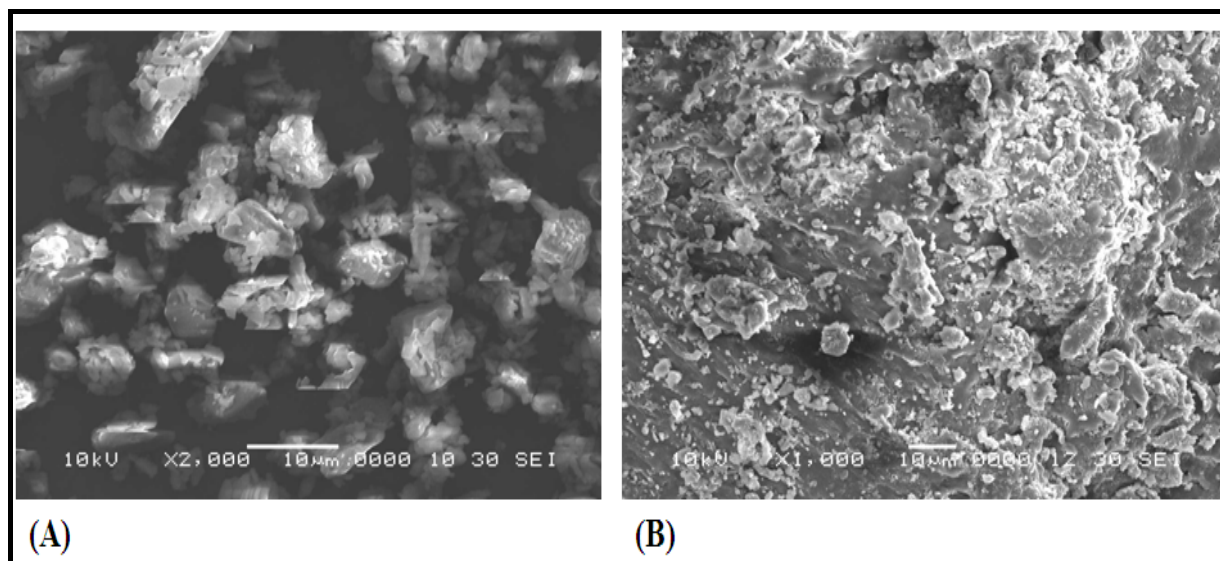


Fig 4. Scanning electron microscopy A) LSP B) SD with Soluplus (1:1)

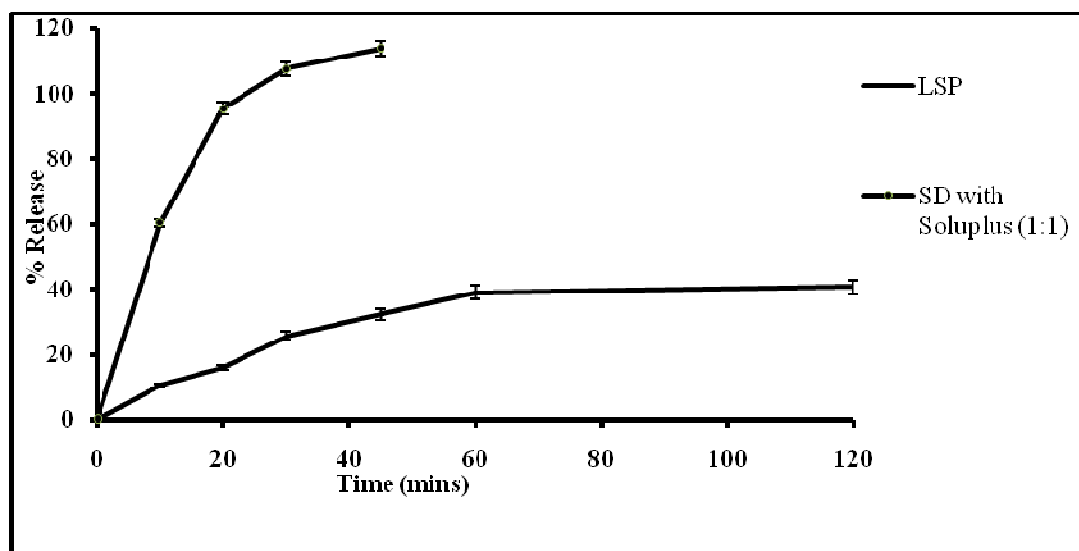


Fig 5. Dissolution profile of LSP and SD with Soluplus (1:1)

CONCLUSION

It can be concluded that use of Soluplus[®] for obtaining SD of LSP proved to be successful. Even though much low amount of Soluplus[®] was used (1:1), significant improvement in solubility and dissolution was observed. Soluplus[®] as a SD carrier imparts good surface adsorbent properties and leaves the drug in amorphous state that increases the surface area, which in turn enhances the dissolution rate. FTIR spectrometry suggested intermolecular hydrogen bonds between LSP and Soluplus[®]. DSC and powder XRD analysis indicated partial amorphization of the drug in SD. Thus this approach has advantage over the existing carriers which require very high amount of the hydrophilic carrier and render the product hygroscopic.

Acknowledgement

Authors would like to thank Wockhardt Limited, Aurangabad, India for providing gift sample of pure drug, Lansoprazole. Authors would also like to thank BASF, Mumbai for providing gift sample of Soluplus[®].

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