ORIGINAL ARTICLE

Lamotrigine Solid Dispersions for Solubility Enhancement

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Abstract

Aim: Lamotrigine is one of the newer antiepileptic drugs, with fewer side effects, which is marketed in the UK since 1992 and introduced in India recently. For epilepsy, it is used to treat partial seizures, primary and secondary tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome. The low aqueous solubility of lamotrigine (0.17 g/L at 25°C) is responsible for its delayed onset of action. The purpose of the present investigation was to increase the solubility and dissolution profile of lamotrigine. **Materials and Methods:** In the present investigation, solubility of lamotrigine pure drug was compared in the presence of Polyethylene glycol 4000 and 6000, respectively. Physical mixture of lamotrigine with PEG 6000 was prepared. Solid dispersions (SDs) of lamotrigine with PEG 6000 were prepared using melting method and characterized for drug-carrier interaction, and SDs were then subjected to dissolution studies. **Results and Discussion:** On the basis of solubility studies, it was found that PEG 6000 has a more pronounced effect on increasing the solubility of lamotrigine as compared to PEG 4000. As indicated from X-ray diffraction pattern and differential scanning calorimetry thermograms, lamotrigine was in the amorphous form in the SDs, which confirmed the better dissolution rate of SDs. **Conclusion:** On the basis of dissolution studies, it was confirmed that the dissolution rate was substantially improved for lamotrigine in its SD as compared to the pure drug and physical mixture. Thus, the SD technique with PEG 6000 as a carrier provides a promising way to enhance the solubility and dissolution rate of lamotrigine.

Key words: Bioavailability, dissolution, lamotrigine, solubility, solid dispersions

INTRODUCTION

Lamotrigine is an anticonvulsant drug used in the treatment of epilepsy and bipolar disorder.[1] For epilepsy, it is used to treat partial seizures, primary and secondary tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome. Chemically unrelated to other anticonvulsants (due to lamotrigine being phenyltriazine), lamotrigine has relatively few side effects and does not require blood monitoring in monotherapy. Lamotrigine also acts as a mood stabilizer.[2] Lamotrigine is rapidly and completely absorbed after oral administration with negligible first-pass metabolism (absolute bioavailability is 98%). Common oral dosage is 25 mg/day (dose/solubility ratio ≥250 ml; Class II drug according to the BCS) peak plasma concentrations occur anywhere from 1.4 to 4.8 h following drug administration and elimination half-life of 24-34 h. This delay in the onset of action in spite of good bioavailability is because of its low aqueous solubility which is only 0.17 g/L.[3]

It is desirable to improve the solubility as well as bioavailability of lamotrigine. The most promising method for promoting dissolution is the formation of solid dispersion (SD) in a proper carrier.[4] The incorporation of drug into solid carriers has been reported to result in an increase in the dissolution of drug leading to improved bioavailability. The SD technique provides a means of reducing particle size to nearly a molecular level. As the soluble carrier dissolves, the insoluble drug is exposed to the dissolution medium as very fine particles for quick dissolution and absorption.[4,5]

Hydrophilic polymers have been widely investigated as carrier substances for SDs. Polyethylene glycol (PEG) is among the most frequently investigated hydrophilic

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polymeric carriers.[6,7] The aim of the present study was to investigate the dissolution of lamotrigine from SDs and to characterize the SDs using infrared spectroscopy, differential scanning calorimetry (DSC), and power X-ray diffractometry. SDs were prepared by melting method technique.

MATERIALS AND METHODS

Materials

Lamotrigine was a gift sample from Organosis Ltd, Noida, U.P., India, and PEG 6000 and 4000 were purchased from Oxford Laboratory, Mumbai, India. All other chemicals and reagents used were of analytical grade.

Methods

Phase solubility studies

Solubility measurements were performed according to the method reported by Higuchi and Connors.[8] Both PEG 4000 and PEG 6000 were assessed for solubility enhancement. Various (1%, 2%, 5%, and 10% w/v) aqueous solutions of PEG 6000 and PEG 4000 were prepared and transferred to volumetric flasks. An excess amount of drug was added to each flask. All flasks were closed with stopper and covered with cellophane membrane to avoid solvent loss. The contents of each flask (10 ml) were equilibrated by shaking for 48 h in a thermostatically controlled water bath at 37 ± 0.1°C (This duration was previously tested to be sufficient to reach equilibrium). After 48 h, samples were filtered through a 0.45 mμ membrane filter. The filtrate was suitably diluted (1 ml diluted up to 25 ml) with corresponding PEG solution and analyzed spectrophotometrically at 304 nm for lamotrigine. Solubility studies were performed in triplicate (n = 3).

Preparation of physical mixtures and SDs

For lamotrigine, the physical mixtures and SDs were prepared by melting method technique in three different ratios using PEG 6000 as a hydrophilic carrier. The following combination of drug and carrier were used [Table 1].

Preparation of SDs by melting method

PEG 6000 was melted in a beaker on a water bath maintained at 50-60°C. The required amount of drug was then added to molten PEG 6000 and mixed thoroughly for 5 min. The molten mixture was cooled rapidly by placing it in an ice bath for about 5 min and solidified. The hardened mixture was powdered, sieved through an 80-mesh screen, packed and stored in desiccators for further estimation. Different ratios of carrier were added, and their optimization was studied on the basis of dissolution and *in vitro* release.

Table 1: Ratio of drug and carrier used for preparation of physical mixture and solid dispersion

Code	Quantity of drug (mg)	Quantity of carrier (PEG 6000) (mg)	Ratio (Drug:Carrier)
SD1	150	750	(1:5)
SD2	150	300	(1:2)
SD3	150	150	(1:1)

PEG: Polyethylene glycol, SD: Solid dispersions

Characterization of physical mixture and SDs of lamotrigine

Fourier transform infrared (FTIR) spectroscopy

FTIR was obtained using Thermo Nicolet 380 FTIR. Samples of lamotrigine, physical mixtures, and SDs were ground and mixed thoroughly with potassium bromide at a 1:5 sample/KBr ratio. The KBr discs were prepared by compressing the powders at a pressure of 5 T for 5 min in a hydraulic press. The scanning range was 40-4000/cm, and the resolution was 4/cm.

Diffrential Scanning Calorimenty (DSC)

The DSC curves were obtained in a Shimadzu DSC-60 cell using aluminum crucibles with about 6.5-10 mg of samples, under dynamic N_2 atmosphere (10 mL min^{-1}) and heating rate of 20°C min^{-1} under a temperature range from 25 to 350°C. The DSC cell was calibrated with indium (mp 156.6°C; ΔH_{fus}=28.54 J g^{-1}) and zinc (mp 419.6°C).

Powder X-ray diffraction (PXRD)

The PXRD patterns were determined for lamotrigine, PEG, and Lamotrigine–PEG 6000 SDs. X-ray diffractograms were obtained using X-ray diffractometer (Bruker, Germany, D8 advance) ceramic X-ray, Cu anode, voltage 2.2 kV, and Detector-Lynx Eye Detector (Silicon Strip Detector Technology). The scanning rate was 1/min over a 2θ range of 1-50. The samples were slightly ground and packed into the aluminum sample container.

In vitro dissolution studies

The dissolution rate studies were performed according to the USP XXVI[9] rotating basket method in a dissolution tester (Nova Ética 299/6, Brazil). The SDs prepared previously were subjected to dissolution studies using USP Paddle Type II apparatus. The dissolution medium used was 0.1 N HCL (PH 1.2)[10] (I.P., 2010) temperature was maintained at 37 ± 0.5°C and paddles rotated at 50 rpm for lamotrigine. Samples of 150 mg of pure drug and SD samples equivalent to 150 mg of drug were filled inside muslin cloth pouches and dropped inside dissolution jars containing 900 ml of dissolution medium. About 10 ml of samples were withdrawn after every 10 min, filtered through membrane filter (pore size 0.45 μm), diluted and analyzed spectrophotometrically at 304 nm for lamotrigine. Fresh medium (10 ml), which was prewarmed at 37°C, was replaced into the dissolution medium after each sampling to maintain its constant volume throughout the test. Dissolution studies were done in

triplicate (n = 3), and calculated mean values of cumulative drug release were used while plotting the drug release graphs.

RESULTS AND DISCUSSION

Phase solubility studies

The effect of carrier concentration on the aqueous solubility of lamotrigine is shown in [Figure 1]. The aqueous solubility of lamotrigine was found to be 0.17 mg/ml. The solubility of the drug was increased up to 35 fold in 10% w/v PEG 6000 aqueous solution at 25°C compared with the pure drug.

The results of the phase solubility as seen from Figure 1 revealed that PEG 6000 has a more pronounced effect on increasing the solubility of lamotrigine as compared to PEG 4000. As the concentration of polymer was increased from 2% to 10%, the solubility of lamotrigine gets increased. However, more pronounced and linear results were obtained from PEG 6000. This can be attributed to more number of ether linkages in the case of PEG 6000 and hence greater solubility. This may be attributed to the improved wetting and solubilizing effect of PEG 6000, which could reduce the interfacial tension between the drug and the dissolution medium.[11]

Fourier transform infrared spectroscopy

Infrared spectroscopy was carried out to elucidate the interaction of lamotrigine with PEG 6000 in the SDs or physical mixtures. The infrared spectra of the physical mixture and the SD together with those for lamotrigine alone and PEG 6000 alone as references are shown in Figure 2.

The spectrum of lamotrigine is characterized by the presence of strong absorption band at 3451/cm, 3318/cm, and 3267/cm, which are all indicative of amines (-NH- group). The carbonyl-stretching mode appears as a very strong doublet at 1600/cm (C=O stretching) and at 800/cm, which was indicative of the presence of aromatic rings.

The spectra of PEG 6000 are characterized by the C-H stretching vibrations at 2883/cm and C-O (ether) stretching at 1105/cm. The careful observation of the IR spectra of pure drug (lamotrigine), and its SD reveals that all the major peaks of the pure drug and PEG 6000 appear with negligible variation in the IR spectrum of the SDs, indicating that there is no chemical interaction between the drug and polymer. From this affirmation, it can be concluded that the drug has maintained its characteristic properties in the SDs prepared by melting method.

Diffrential Scanning Calorimenty

The DSC curve of pure drug lamotrigine shows an endothermic peak at 224.76°C indicating that it has a sharp melting point, whereas PEG 6000 displays a peak at 74.79°C [Figure 3]. In the melting method, both the drugs as well as the polymer show a slight shift in the peaks indicating amorphization of the drug in the polymer.[11] The endothermic thermogram of the pure drug in the formulation has slightly changed its shape and become bit broad in the formulation. Perhaps, it may be due to the reason that the pure drug must have become more amorphous in the formulation which may be helpful in increasing the solubility of the pure drug in the formulation.[11]

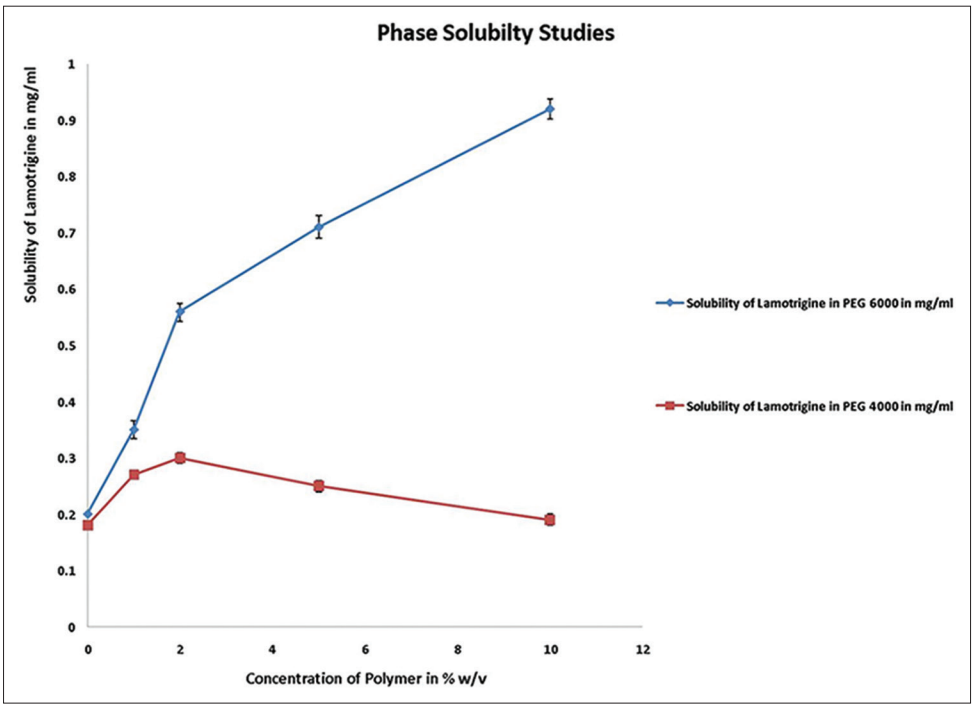

Figure 1: Effect of polyethylene glycol 6000 and 4000 on the solubility of lamotrigine

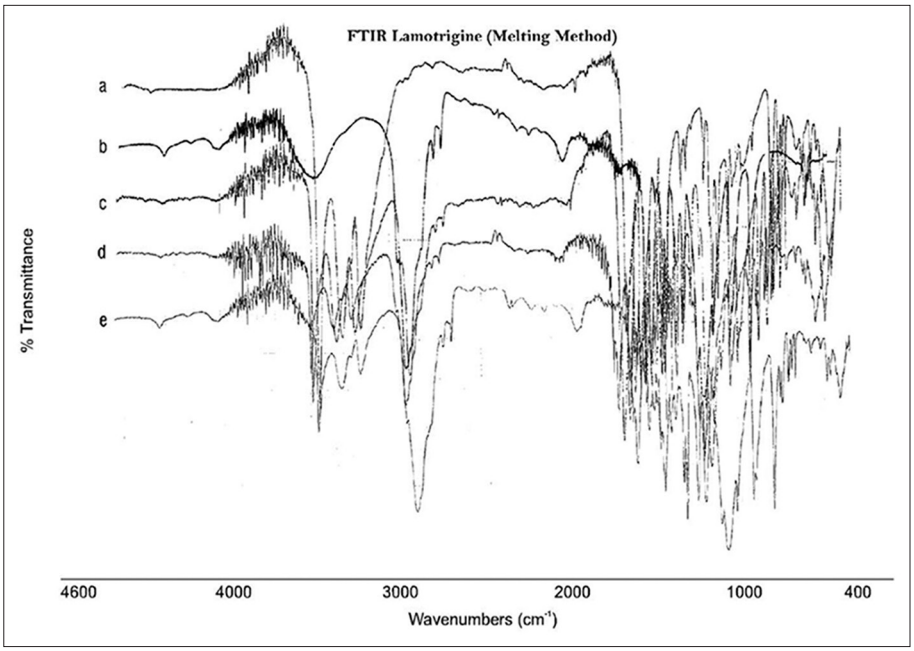

Figure 2: Fourier transform infrared curves. (a) Pure drug lamotrigine, (b) polyethylene glycol, (c) solid dispersions 1 (SD1), (d) SD2, (e) SD3

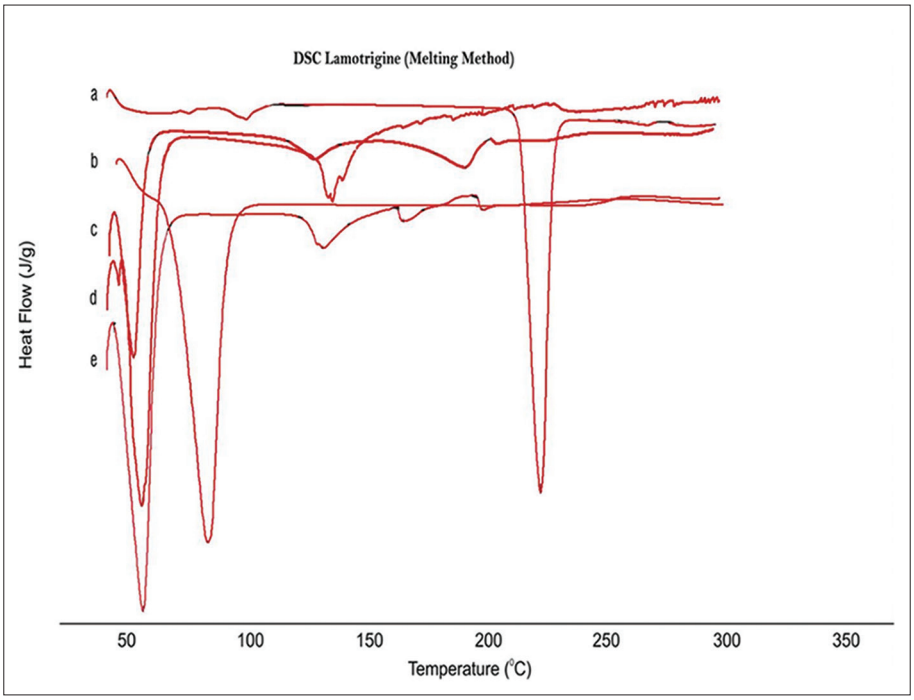

Figure 3: Differential scanning calorimetry thermogram. (a) Pure drug lamotrigine, (b) polyethylene glycol, (c) solid dispersions 1 (SD1), (d) SD2, (e) SD3

Powder X-Ray Diffraction

The solid state crystallinity of lamotrigine, PEG 6000 and formulations prepared by melting method technique were studied by PXRD technique [Figure 4]. The reduction in crystallinity of lamotrigine in the formulations was observed, and it was also noted that the crystallinity was decreased with increase in the concentration of PEG 6000 (1:1, 1:2, 1:5).

In vitro dissolution studies

The dissolution profile of lamotrigine, physical mixture, and SDs are illustrated in Figure 5. Both physical mixtures and SDs showed enhanced dissolution rate as compared to the pure drug. Drug release was further enhanced by the solid dispersions SD1 (1:5), SD2 (1:2), and SD3 (1:1). SD1 showed a drug release of 57.47 ± 0.99%, whereas

SD2 and SD3 showed a drug release of 26.85 ± 1.3% and 30.13 ± 2.5%, respectively, at the end of 60 min. Maximum drug release was observed when lamotrigine was combined with PEG 6000 in 1:5 ratio for SD prepared by the melting method. SDs increased the solubility and maximizing the surface area of the drug that came in contact with the dissolution medium as the carrier dissolved. This might be due to the surface tension lowering effect of polymer to the medium, resulting in the wetting of hydrophobic drug of crystalline surface, which can be attributed to the reduction of crystallinity of drug, and therefore, improved release profile (supported by X-ray diffraction), reduction of particle size to molecular level, and expansion of the surface area for dissolution.[12]

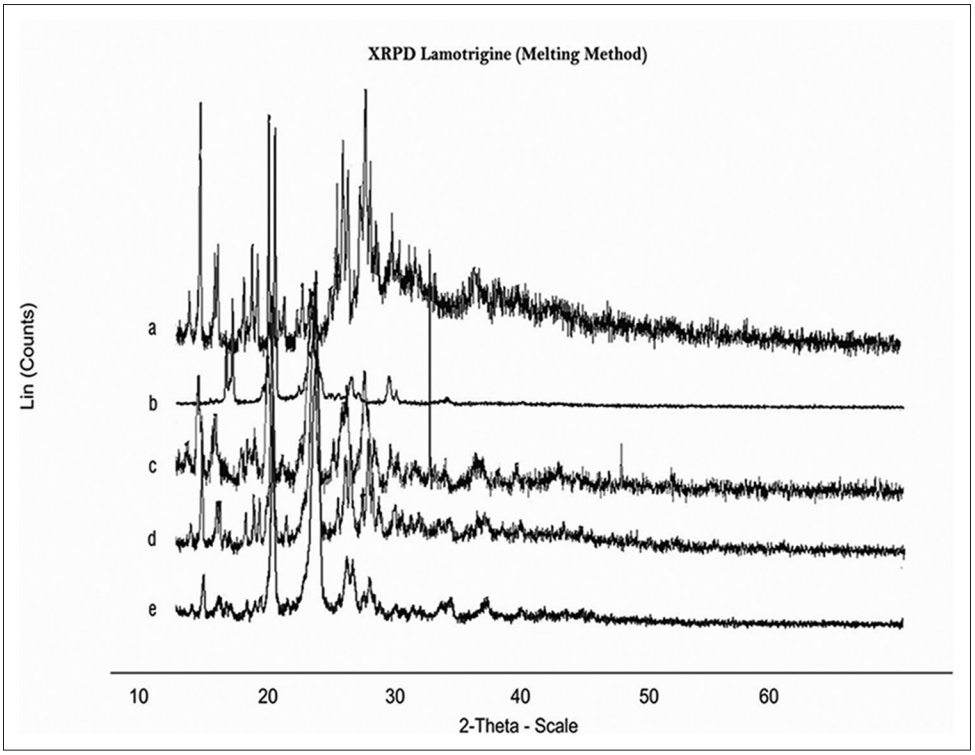

Figure 4: Powder X-ray diffraction. (a) Pure drug lamotrigine, (b) polyethylene glycol, (c) solid dispersions 1 (SD1), (d) SD2, (e) SD3

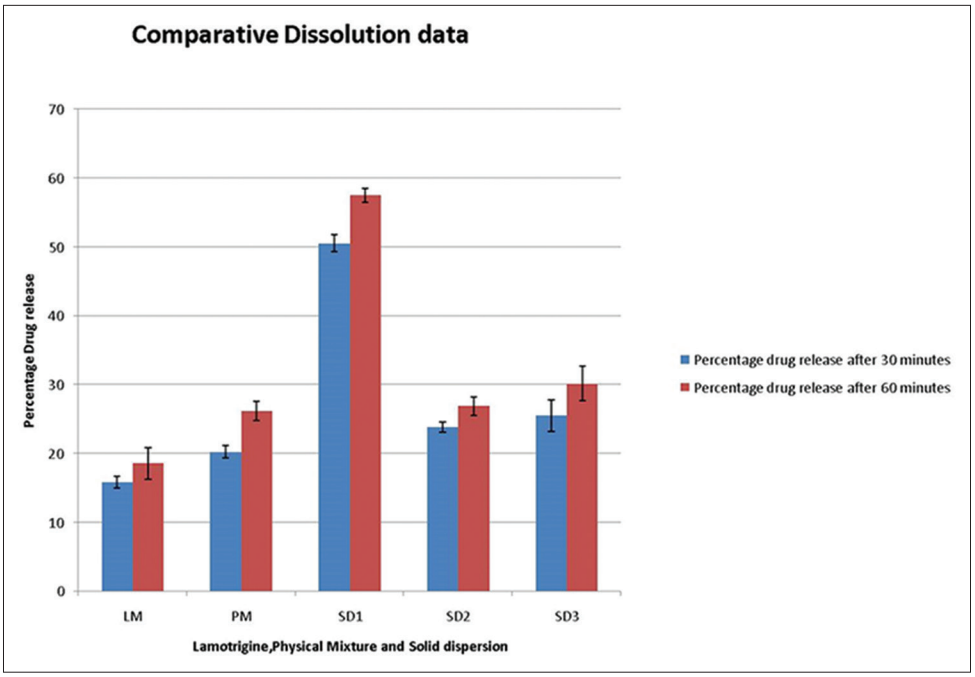

Figure 5: Comparative dissolution data lamotrigine

From Figure 5, it is evident that the dissolution rate of lamotrigine has improved in the case of SD, and the best dissolution profile was obtained when drug and carrier were combined in 1:5 ratio

CONCLUSION

SDs, prepared from hydrophilic polymers using the melting method, were effective in improving drug dissolution. The above studies indicated that PEG 6000 inhibited the crystallization of drug, resulting in the amorphous state form of the drug in SD. The dissolution rate of lamotrigine from SD was dependent on the concentration of the carrier. Dissolution of drug decreased with an increase in carrier content and the highest dissolution rate was observed when the drug and the carrier were combined in 1:5 ratio. PXRD and DSC results have confirmed the amorphous state of the drug in SD.

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