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Improvement of dissolution properties of lamotrigine by inclusion complexation and solid dispersion technique

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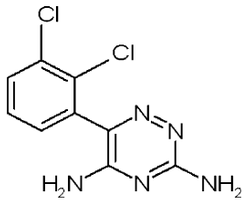
The aim of the present work was to improve the dissolution characteristics of the poorly water soluble antiepileptic drug lamotrigine (LMN) by inclusion complexation using hydroxy propyl β-cyclodextrin (HP β-CD) by co-evaporation technique and by, solid dispersion, prepared by the melt method using poloxamer 407 (L 127). Phase solubility studies showed A_L type curves with both the carriers. Dissolution of LMN was significantly improved ($p < 0.05$) by inclusion complexation and solid dispersion preparation. Results of solid state characterization performed by Fourier Transform Infrared Spectroscopy, Differential Scanning Calorimetry and Powder X-ray Diffractrometry techniques revealed a decrease in the crystallinity of LMN that might be accounting for improvement in the dissolution properties as seen from dissolution studies.

1. Introduction

Advances in technologies have increased the number of new drug molecules, among which about 40% suffer from poor aqueous solubility (Fahr and Liu 2007). For drugs having poor aqueous solubility and high permeability (BCS Class II), dissolution is the determinant for the rate and extent of drug absorption from the gastrointestinal tract (Horter and Dressman 2001). Thus improvement of drug dissolution is desirable to improve the bioavailability of poorly water soluble drugs. Among the various techniques used for the improvement in the drug dissolution characteristics, inclusion complexation with cyclodextrins (Nalluri et al. 2003; Chowdary and Rao 2001) and solid dispersions (Serajuddin 1999; Craig 2002) have been frequently used.

Hydroxy propyl β cyclodextrin (HP β-CD), a cyclic oligosaccharide derived from β-CD, having hydrophobic outer region and hydrophilic inner cavity enabling to produce soluble complexes with A_L type curves (Challa et al. 2005). Thus, HP β-CD was selected for complexation with lamotrigine (LMN) and it has also been successfully used for improving the dissolution characteristics of poorly water soluble drugs (Chowdary and Rao 2001; Yamamoto et al. 2000; Cappello et al. 2006; Patel et al. 2008). Recently, Poloxamer 407 (L 127), a non ionic surfactant, has been employed for the preparation of solid dispersions to improve dissolution of poorly water soluble drugs (Yamamoto et al. 2000; Ahuja et al. 2007). L 127 is a amphiphilic polymer having the ability to form micelles which facilitates the solubillization of poorly water soluble drugs.

Lamotrigine (6-(2, 3-dichlorophenyl)-1, 2, 4-triazine-3, 5-diamine, LMN, Fig. 1) an antiepileptic drug is shown to be effective in partial, generalized and tonic clonic seizures (O'Donnell and Bateman 2000). It has poor aqueous solubility (0.17 mg/ml at 25 °C) (The Internet Drug Index) which could be the rate determing step for its efficient absorption and thus various researchers have tried to improve the solubility and dissolution rate of LMN to improve its therapeutic efficacy (Shinde et al. 2008; Shah et al. 2009).



In our previous work, inclusion complexes of LMN were prepared with HP β-CD utilizing the kneading method (Shah et al. 2009), and the technique was successful in improving the dissolution properties of LMN. In the present work attempt was done to improve the dissolution characteristics of LMN by inclusion complexation with HP β-CD by using the coevaporation technique and by preparing solid dispersions of LMN with surfactant based polymer, L 127. Inclusion complexation by coevaporation method has been successfully done for dissolution enhancement of poorly water soluble drugs (Yamamoto et al. 2000; Patel et al. 2008). In order to determine the underlying principle for improved drug release, the promising systems of both carriers were characterized by Fourier Transform Spectroscopy (FT-IR), Differential Scanning Calorimetry (DSC) and Powder X-ray Diffraction Analysis (PXRD).

2. Investigations, results and discussion

2.1. Phase solubility studies

The phase solubility diagram of LMN with HP β-CD and L 127 is shown in Fig. 1. The plot suggested linear relationship ($r^2 > 0.99$) between solubility of LMN and concentration of carriers. The solubility increased linearly indicating A_L type solubility curve; with slope less than 1, thus, 1:1 molar complexation of LMN with HP β-CD (Higuchi and Connors 1965) and

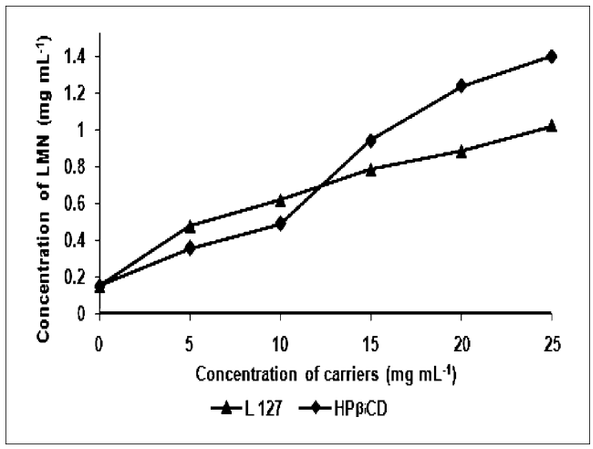


Fig. 1: Phase solubility curves of LMN

Table 1: Values of Gibb's free energy of transfer, ΔG°_{tr} for solubilization process of LMN in the aqueous solutions of carriers

Conc. of carrier mg ml^{-1}	ΔG°_{tr} kJ/mole for water-soluble carriers at 25 °C	
	HP β-CD	L 127
5	−0.907	−1.225
10	−1.251	−1.506
15	−1.965	−1.767
20	−2.258	−1.892
25	−2.389	−2.048

1:1 LMN-L 127 interaction (Ahuja et al. 2007) was suggested. The improvement in drug solubility might be attributed to a better surface activity of L 127 (Yamamoto et al. 2000; Ahuja et al. 2007), and due to 1:1 complex formation between LMN and HP β-CD (Ruan et al. 2005). The obtained values of ΔG_{tr}° are shown in Table 1. The negative values of calculated Gibbs free energy transfer indicated the spontaneous solubilization of LMN in aqueous solution of polymers.

2.2. Percentage drug content

Percentage drug content was found in the range of 98.44 ± 0.24 and 99.14 ± 0.24 for inclusion complexes and 98.62 ± 0.49 and 97.76 ± 0.73 for solid dispersion. All determinations are mean $\pm$ S.D., n = 3.

2.2.1. In vitro dissolution studies

Dissolution curves of LMN from various examined binary systems are shown in Fig. 2. The dissolution profile was plotted as percentage drug release versus time. As shown in Fig. 2a the dissolution profiles of LMN with HP β-CD at different drug to carrier ratios, physical mixture (1: 0.25) and LMN alone, depicted significant improvement ($p < 0.05$) in the drug dissolution by preparation of coevaporates which might be attributed to inclusion complex formation (Patel et al. 2008; Ruan et al. 2005). The improvement in the drug dissolution by physical mixture might be due to improved drug wettability. As depicted in Fig. 2b the dissolution profile of LMN with L 127, it was evident that dissolution was significantly improved ($p < 0.05$) by the preparation of solid dispersion of LMN. Even with physical mixture the dissolution rate was improved. The increased dissolution properties of LMN might be attributed to the micellar solubilization due to L 127 (Ahuja et al. 2007). However, no appreciable difference was observed in dissolution with increase in the concentration of the carrier. Values of percentage of drug release in 10 (DP_{10}) and 30 (DP_{30}) min and are shown in Table 2. Improvement in the dissolution characteristics of LMN was obtained by both formation of solid dispersions and inclusion complexes.

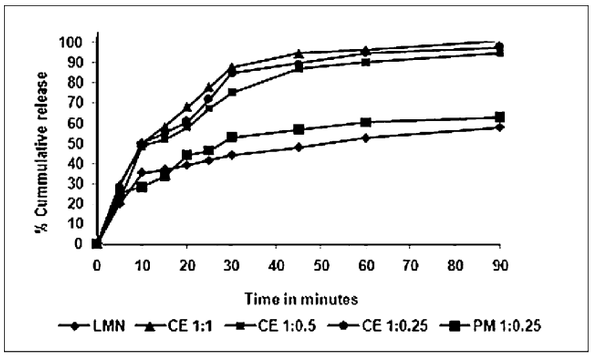
Table 2: Values of % drug dissolved from various samples in 10 (DP_{10}) and 30 (DP_{30}) minutes

Samples	DP_{10}	DP_{30}
LMN	35.20	43.86
1:0.25 LMN:HP-βCD	49.69	84.49
1:0.50 LMN:HP-βCD	48.50	74.81
1:1 LMN:HP-βCD	49.98	87.54
1:0.25 LMN:HP-βCD PM	28.07	52.67
1:1 LMN:L 127	72.29	93.21
1:2 LMN:L 127	73.98	89.04
1:1 LMN:L 127 PM	39.63	54.14

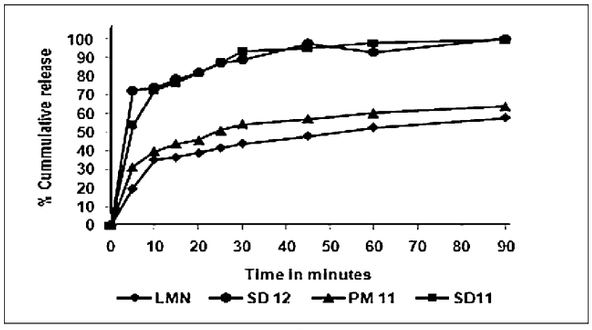
*PM physical mixture

2.3. Fourier Transform Infrared (FT-IR) spectroscopy analysis

Fig. 3 illustrates the FT-IR spectra of LMN, carriers and respective binary systems. The IR spectra of LMN (Fig. 3a) is characterized by principal absorption peaks at 3447 cm^{-1} (N–H stretching); 3208 cm^{-1} (C–H stretching); 1619 cm^{-1} (C = N); 1319 cm^{-1} (C–N); 1556 cm^{-1} (C = C stretching); 1053 cm^{-1} (C–Cl); 738 cm^{-1} (o substituted benzene); 747, 795 and 959 cm^{-1} (m substituted benzene). The IR spectrum of HP β-CD (Fig. 3d) showed prominent peaks at 3414 cm^{-1} (O-H stretching vibrations); 2928 cm^{-1} (C-H stretching vibrations); 1647 cm^{-1} (H-O-H bending); 1034 cm^{-1} and 1083 cm^{-1} (C-H,



(a)



(b)

Fig. 2: *In vitro* dissolution of LMN CE, coevaporates (a) and SD, solid dispersions (b); PM physical mixture

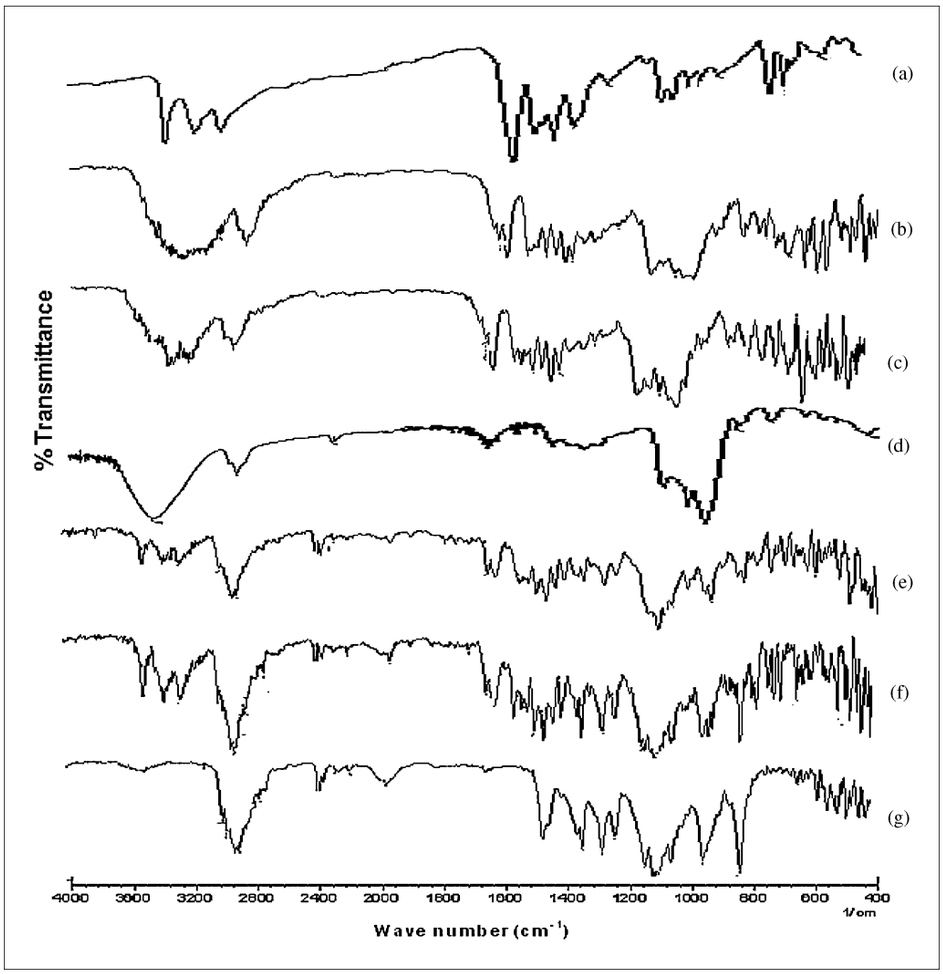


Fig. 3: FTIR spectra of LMN, carriers and its binary systems; (a) LMN, (b) CE 1:0.25, (c) PM 1:0.25, (d) HP β-CD, (e) SD 1:1, (f) PM 1:1, (g) L 127, CE coevaporates; SD solid dispersions; PM physical mixture

C-O stretching vibrations). L 127 (Fig. 3g) showed characteristic peaks, at 2969, 2884 and 2865 cm^{-1} (C-H stretch), 1468 and 1467 cm^{-1} (C-H bending) and, 1343, 1239, 1280, 1145, 1117, and 1061 cm^{-1} (C-O stretching). The IR spectra of physical mixtures (Fig. 3c, 3f) showed spectra corresponding to a superposition of the parent products. In both the binary systems, (Fig. 3b, 3e) the N-H stretching band of LMN at 3447 cm^{-1} disappeared suggesting intermolecular hydrogen bonding between LMN and carriers (Yamamoto et al. 2000; Ruan et al. 2005).

2.4. Differential Scanning Calorimetry (DSC) analysis

DSC curves of LMN, carriers and respective binary systems are shown in Fig. 4. DSC thermogram of pure LMN (Fig. 4a) showed an endothermic peak at 219.6 °C, representing the melting point of crystalline LMN. DSC spectra of HP β-CD (Fig. 4d), showed an endothermic peak at 80.59 °C, indicating loss of water content (Ruan et al. 2005). DSC spectra of L 127 (Fig. 4g) showed an endothermic peak at 53.18 °C corresponding to its melting point. In DSC spectra of physical mixture (Fig. 4c, 4f), the melting peak of drug was decreased slightly. Both the binary systems (Fig. 4b, 4e) showed decrease in the intensity of crystalline drug peak, suggesting decrease in the crystallinity of LMN. An analogous observation was obtained by other investigators (Yamamoto et al. 2000). Thus, decrease in drug crystallinity might be responsible for the enhancement of drug dissolution which was further evaluated by PXRD analysis.

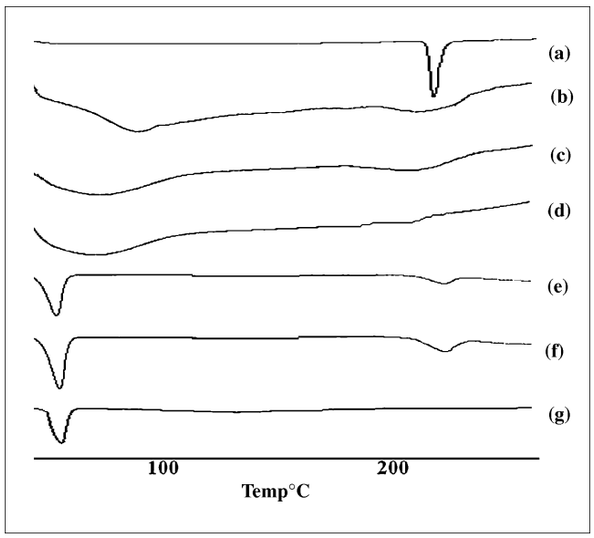


Fig. 4: DSC spectra of LMN, carriers and its binary systems; (a) LMN, (b) CE 1:0.25, (c) PM 1:0.25, (d) HP β-CD, (e) SD 1:1, (f) PM 1:1, (g) L 127, CE coevaporates; SD solid dispersions; PM physical mixture

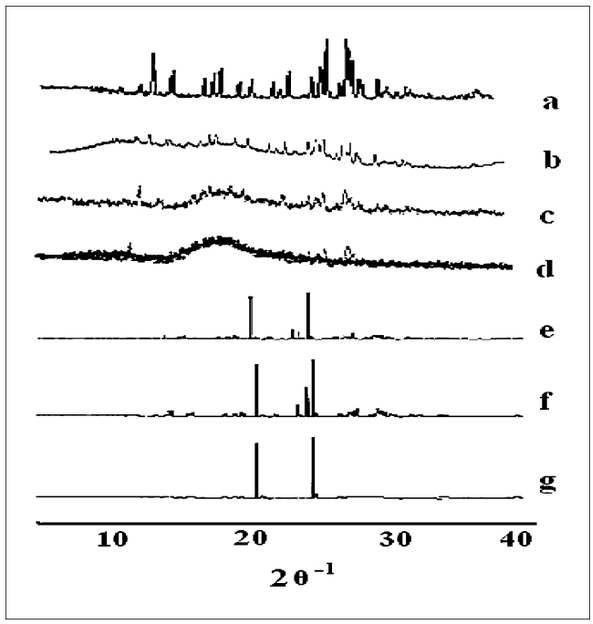


Fig. 5: PXRD spectra of LMN, carriers and its binary systems; (a) LMN, (b) CE 1:0.25, (c) PM 1:0.25, (d) HP β-CD, (e) SD 1:1, (f) PM 1:1, (g) L 127, CE coevaporates; SD solid dispersions; PM physical mixture

2.5. Powder X-ray Diffraction (PX-RD) analysis

Fig. 5 illustrates the PXRD spectra of LMN, carriers and respective binary systems. The PXRD pattern of LMN (Fig. 5a) showed sharp and intense peaks indicating its crystalline nature. LMN showed major peak at 2θ values of 5.05, 5.59, 12.45, 26.75 and 29.41. Due to the amorphous nature of HP β-CD (Fig. 5d), no sharp peaks were observed in the spectra of HP β-CD. PXRD pattern of L 127 (Fig. 5g) showed two salient peaks at 19.05° and 23.30°. Physical mixtures (Fig. 5c, 5f) the crystalline peaks were somewhat decreased. In prepared binary systems (Fig. 5b, 5e) the peaks are of decreased intensity, indicating the decreased crystallinity of the drug (Yamamoto et al. 2000), which supports the finding obtained in DSC study.

3. Experimental

3.1. Materials

LMN was kindly donated by Rantus Pharma Pvt. Ltd. (Hyderabad, India). HP β-CD and L 127 were gifts from Gangwal Chemicals Pvt. Ltd. (Mumbai, India) and BASF Ltd. (Mumbai, India) respectively. All other reagents used were of analytical grade. Double distilled water was used throughout the work.

3.2. Phase solubility studies

Phase solubility studies were carried out in distilled water according to the method of Higuchi and Connors (1965). Excess quantity of LMN (50 mg) was added to 25 ml of aqueous solutions of various concentrations of carriers. The suspensions were shaken at 25 °C for three days. The samples were filtered through whatman filter paper (0.12 μm), diluted suitably and assayed spectrophotometrically at 306 nm (UV-1700 Shimadzu, Japan). The apparent 1:1 stability constant was calculated from the phase solubility graph according to the Eq. (1),

$$K_s = \frac{Slope}{S_o(1 - slope)} \quad (1)$$

where S_o is the solubility of LMN in absence of polymer.
Gibb's free energy of transfer (ΔG_{tr}°) of LMN from pure aqueous media to solution of polymer was calculated using the Eq. (2),

$$\Delta G_{tr}^{o} = -2.303RT \log \left(\frac{S_o}{S_s}\right) \quad (2)$$

where, S_o/S_s is the ratio of the solubility of LMN in aqueous solution of polymer to that of the pure distilled water.

3.3. Preparation of solid binary systems

3.3.1. Preparation of co-evaporates of LMN and HP β-CD

Coevaporates were prepared in 1:0.25, 1:0.5 and 1:1 drug to carrier ratios. Methanol was used as a solvent for coevaporation. LMN was first dissolved in methanol with the help of sonication and then HP β-CD was added, the solvent was allowed to evaporate on the stirrer at a temperature between 45–50 °C. The resultant solid was pulverized and stored in desiccators until further use.

3.3.2. Preparation of solid dispersions of LMN and L 127

Solid dispersions of LMN with L 127 were prepared by melt method in 1:1 and 1:2 drug to carrier ratios. The carrier was melted in the petridish and drug was dispersed in the molten mass. The mass was cooled at room temperature, sieved and stored in desiccators until further study.

3.3.3. Preparation of physical mixtures

Physical mixtures were prepared by blending individual constituents in the glass mortar in the mentioned ratios.

3.4. Determination of drug content

Drug content was determined by dissolving an accurately weighed quantity of binary systems of LMN in methanol. Then the solution was filtered, appropriately diluted and concentration was measured spectrophotometrically at 306 nm.

3.5. In vitro dissolution studies

In vitro dissolution studies of LMN, physical mixtures, coevaporates and solid dispersions were carried out using a dissolution test apparatus USP Type I at 100 rpm (Electrolab dissolution tester USP, TDT 06P, Mumbai, India) using 900 ml 0.1N HCl at 37 ± 0.5 °C (USFDA Guidelines). Samples equivalent to 25 mg LMN were placed in the basket. At specified time intervals, a 5 ml sample was withdrawn and replaced by the fresh media. The samples were then filtered and the content was determined spectrophotometrically at 266 nm. The study was done in triplicate and the results obtained from dissolution studies were validated statistically.

3.6. Fourier Transform Infrared (FT-IR) Spectroscopic analysis

Powder samples of LMN, carrier and its binary systems were characterized using a FT-IR spectrophotometer (Shimadzu 8400, Japan) by the potassium bromide (KBr) pellet method. The scanning range was 4000 to 400 cm^{-1} at resolution of 1 cm^{-1}. An average of 20 scans is reported.

3.7. Differential Scanning Calorimetry (DSC) analysis

DSC spectra of samples were taken using DSC (Shimadzu, DSC 60 TSW 60, Japan). Accurately weighed samples crimped in aluminum pans were heated from 30 to 250 °C, at a scanning rate of 10 °C/min in air atmosphere. Empty sealed aluminum pan was used as reference.

3.8. Powder X-ray Diffraction (PXRD) analysis

PXRD patterns of LMN, carriers and binary systems were recorded using X-ray diffractometer (X-pro Pan analytical, Phillips, Mumbai, India) with a copper tube anode over the interval 1–40° $2\theta^{-1}$. The operation data were as follows: generator tension (voltage) 40 kV; generator current 30 mA; scanning speed 2° min^{-1}.

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