JPP Journal of Pharmacy and Pharmacology

JPP 2008, 60: 1121–1129

Received January 2, 2008
Accepted May 6, 2008
DOI 10.1211/jpp.60.9.0002
ISSN 0022-3573

Enhanced solubility and dissolution rate of lamotrigine by inclusion complexation and solid dispersion technique

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Abstract

The solid-state properties and dissolution behaviour of lamotrigine in its inclusion complex with β-cyclodextrin (βCD) and solid dispersions with polyvinylpyrrolidone K30 (PVP K30) and polyethyleneglycol 6000 were investigated. The phase solubility profile of lamotrigine with βCD was classified as A_L-type, indicating formation of a 1:1 stoichiometry inclusion complex, with a stability constant of $369.96 \pm 2.26\ M^{-1}$. Solvent evaporation and kneading methods were used to prepare solid dispersions and inclusion complexes, respectively. The interaction of lamotrigine with these hydrophilic carriers was evaluated by powder X-ray diffractometry, Fourier transform infrared spectroscopy and differential scanning calorimetry. These studies revealed that the drug was no longer present in crystalline state but was converted to an amorphous form. Among the binary systems tested, PVP K30 (1:5) showed greatest enhancement of the solubility and dissolution of lamotrigine.

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Acknowledgements: The authors are grateful to Shivaji University, Kolhapur, Maharashtra, India for providing differential scanning calorimetry, infrared spectroscopy and powder X-ray diffractometry facilities, and to the Principal of the Govt. College of Pharmacy, Karad, Maharashtra, India for providing laboratory facilities and constant encouragement.

Introduction

Lamotrigine (6-(2,3-diclorophenyl)-1,2,4-triazine-3,5-diyldiamine) is used for the prevention of tonic–clonic epileptic seizures (Sweetman 2002) and is also effective against partial seizures, primary and secondary generalized seizures, absence seizures and other types of epileptic seizures (Perucca 2000). Its primary mechanism of action is blocking voltage-dependent sodium channels, leading to inhibition of excitatory neurotransmitter release and stabilization of neuronal membranes (Chong & Dupuis 2002). Although lamotrigine has gained widespread acceptance in the treatment of seizures, its poor aqueous solubility ($0.17\ mg\ mL^{-1}$ at 25°C; The Internet Drug Index 2007) limits its absorption and dissolution rate and thus delays onset of action (Hurley 2002).

The dissolution of drugs is a prime determinant in the absorption of poorly water-soluble drugs and also serves as a rate-limiting step (Horter & Dressman 1997). Improvements in the apparent solubility and/or dissolution rate of a poorly water-soluble drug through the formation of an inclusion complex or solid dispersion technique may enhance its bioavailability. Various techniques have been used to enhance the solubility/dissolution rate of poorly water-soluble drugs, including the use of surfactants (Schott et al 1982), inclusion complexation (Veiga et al 1996), use of polymorph (Henck et al 1997), drug micronization into an amorphous form (Hancock & Zografi 1997) and solid dispersion (Chiou & Riegelman 1971; Serajuddin 1999; Christian & Dressman 2000). Among them, inclusion complexation with cyclodextrins and the solid dispersion technique are most frequently used.

Cyclodextrins have attracted the attention of many formulation experts because of their hydrophilic nature and ability to form stable inclusion complexes with properly sized guest molecules (Longxiao & Suyan 2006), increasing the aqueous solubility and providing a driving force for the diffusion of lipophilic drugs across biological membranes (Loftsson & Bodor 1995; Mar et al 1999; Bruce 2000; Gian et al 2002) but without altering the molecular structure or permeability characteristics (Brun et al 2006). Complexation with cyclodextrins has been used extensively to enhance the aqueous solubility and dissolution rate of poorly water soluble drugs (Vandelli et al 1995; Archontaki et al 2002; Fernandes et al 2002). Cyclodextrins act as excellent carriers for hydrophobic drug molecules in the solution

phase, delivering them to the surface of biological membranes (Masson et al 1999).

In solid dispersion, hydrophilic polymers such as polyvinylpyrrolidone (PVP) and polyethyleneglycol (PEG) have been widely used as carriers because of their low cost and high aqueous solubility. Both polymers are freely soluble in water and are available in various molecular weights, ranging from 10000 to 700000 for PVP and from 200 to 300000 for PEG. The molecular size of both polymers favours the formation of interstitial solid solutions (Tantishaiyakul et al 1999; Trapani et al 1999; Franco et al 2001; Verheyen et al 2002; Sethia & Squillante 2004; Sammour et al 2006). The solubilization of drugs from solid dispersion systems is mainly attributed to the reduction in particle size, increase in surface area and reduction in crystallinity, which together improve the dissolution rate. Furthermore, no energy is required to break up the crystal lattice of a drug during the dissolution process, and drug solubility and wettability may be increased by surrounding hydrophilic carriers (Bruce 2000).

The aim of this work was to improve the aqueous solubility and dissolution rate of lamotrigine using inclusion complexation and solid dispersion techniques using various hydrophilic carriers such as β-cyclodextrin (βCD), PVP K30 and PEG 6000. The inclusion complex of lamotrigine with βCD was prepared in equimolar ratios by a kneading method. The physical mixture of lamotrigine–βCD in 1:1 molar ratio was prepared by mixing the individual components.

The solubility type and the stability constant of the complex were established in phase solubility studies. Solid dispersion systems of lamotrigine were prepared with PVP K30 and PEG 6000, each in 1:1, 1:3 and 1:5 ratios, using a solvent method. Different ratios of polymers were selected on a purely random basis. Powder X-ray diffractometry (XRD), Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) were used to characterize the solid-state properties of lamotrigine, the physical mixture, inclusion complex and solid dispersions. The aqueous solubility and dissolution behaviour of pure lamotrigine and all its binary systems were evaluated further.

Materials and Methods

Materials

Lamotrigine was a gift from Lupin Ltd (Mumbai, India). βCD was kindly supplied by Panacea Biotech (Chandigad, India). PVP K30 was a gift from Signet Chem. Lab. (Mumbai, India). PEG 6000 was purchased from Loba Chemie (Mumbai, India). All reagents were of analytical grade. Double-distilled water was used throughout.

Phase solubility studies of lamotrigine with βCD

Phase solubility studies were carried out in distilled water in triplicate according to the method described by Higuchi and Connors (1965). Excess lamotrigine (50 mg) was added to 20 mL aqueous solutions containing various concentrations of βCD (0–0.01 M). The suspensions were then shaken on a rotary shaker at 25 ± 2°C for 4 days. Once equilibrium was achieved, the samples were filtered through a 0.45 μm membrane filter and diluted. The concentration of lamotrigine was determined spectrophotometrically at 307 nm. The apparent stability constant Ks was calculated from phase solubility graphs with the assumption of 1:1 stoichiometry according to the following equation: $K\text{s} = slope / S_0 (1 - slope)$, where S_0 is the solubility of lamotrigine in the absence of cyclodextrin.

Preparation of solid binary systems

Preparation of physical mixture of lamotrigine with βCD

The physical mixture of lamotrigine–βCD in 1:1 molar ratio were prepared by mixing individual components that had previously been sieved through size-60 mesh.

Preparation of inclusion complex of lamotrigine with βCD

Lamotrigine and βCD in a 1:1 molar ratio were weighed accurately and transferred to a mortar. The mixture was then triturated with a small volume of water/ethanol (1:1 v/v) solution to form a homogenous paste. The paste was kneaded for 45 min and then dried at 40°C in an oven for 24 h. The final product was pulverized and sieved through size-60 mesh.

Preparation of solid dispersions of lamotrigine by solvent evaporation

Solid dispersions of lamotrigine were prepared by solvent evaporation. Lamotrigine and water-soluble polymers in different ratios were weighed accurately and transferred to a beaker containing methanol. The solvent was then evaporated in a vacuum evaporator and the resulting solid dispersions were collected and stored in desiccators until they attained constant weight. The solidified masses were crushed, pulverized and passed through size-60 mesh.

XRD studies

The XRD patterns of pure lamotrigine and all binary systems of lamotrigine with βCD and hydrophilic polymers were recorded using a Philips Analytic X-Ray – PW 3710 diffractometer (Philips, Almelo, The Netherlands) with a copper tube anode over the interval 5–70° $2\theta^{-1}$. The operation data were as follows: generator tension (voltage) 40 kV; generator current 30 mA; scanning speed 2° min^{-1}.

FTIR studies

Infrared spectra were obtained using a Perkin-Elmer Spectrum-one FTIR spectrometer (Shelton, CT, USA) using KBr disks. The samples were previously ground and mixed thoroughly with KBr. The KBr disks were prepared by compressing the powder. The scanning range was kept from 4000 to 450 cm^{-1} and the accumulations were 4.

DSC studies

DSC measurements were performed on a TA SDT 2960 DSC differential scanning calorimeter (TA instruments, New Castle, DE, USA). The accurately weighed sample was placed in an

aluminium pan. An empty aluminium pan was used as a reference. The experiment was carried out in nitrogen atmosphere (flow rate 100 mL min^{-1}) at a scanning rate of 10°C min^{-1} in the range of 0–350°C.

Determination of percentage drug content

Drug content was determined by dissolving solid dispersions equivalent to 10 mg of drug in 10 mL methanol following by ultrasonication for 20 min. The volume was adjusted to 100 mL with distilled water. The solution was filtered through Whatman filter paper no. 41, suitably diluted, and the absorbance measured at 307 nm using a double-beam UV spectrophotometer. The amount of complexed drug in the kneaded product was determined using an ethanol:water mixture (1:9) as the solvent.

Saturation solubility studies

Saturation solubility studies were performed in triplicate according to the method reported by Higuchi and Connors (1965). Excess of pure drug, physical mixture, inclusion complex or solid dispersions were added to 20 mL distilled water in a screw-cap tube and shaken in a rotary flask shaker at room temperature (25°C) for 24 h. (Preliminary studies had shown that equilibrium solubility was achieved in 24 h.) Once equilibrium had been achieved, appropriate aliquots were withdrawn and filtered through Whatman filter paper no. 41 and the filtrate analysed spectrophotometrically at 307 nm.

Dissolution studies

The dissolution rate of lamotrigine alone, physical mixture, inclusion complex and solid dispersions was measured in triplicate in a dissolution apparatus (Lab India, Model Disso 2000 Tablet dissolution test apparatus, Mumbai, India) using the paddle method, according to USP Type II. Dissolution studies were carried out using 900 mL 0.1M HCl at 37 ± 0.5°C at 50 rev min^{-1} (US FDA guidelines). Twenty-five mg lamotrigine, or its equivalent amount of formulations, were added to 900 mL 0.1M HCl. Five mL samples were withdrawn after 5, 10, 15, 20, 25, 30, 45, 60 and 90 min and replaced each time with 5 mL fresh 0.1M HCl. The solutions were immediately filtered through 0.45 μm membrane filter, diluted and the concentration of lamotrigine determined spectrophotometrically at 265 nm. The results obtained from the dissolution studies were validated statistically using the Kruskal–Wallis test followed by non-parametric post-hoc test (e.g. Dunn's test (n = 3)).

Results and Discussion

Phase-solubility studies of lamotrigine with βCD

The phase-solubility graph for the complex formation between lamotrigine and βCD is shown in Figure 1. This plot shows that the aqueous solubility of the drug increases linearly as a function of βCD concentration. The phase solubility profile of lamotrigine with βCD can be classified as A_L-type. The linear host–guest correlation coefficient $r = 0.9940$ ($r^2 = 0.9880$) with a slope of 0.1984 suggested the formation of a 1:1 complex with respect to βCD concentration (Higuchi & Connors 1965). The equation from the linear regression analysis was $y = 0.1984x + 0.00067$. The apparent stability constant, $K_{1:1}$, obtained from the slope of the linear part of the phase solubility graph, was 369.96 ± 2.26 M^{-1}.

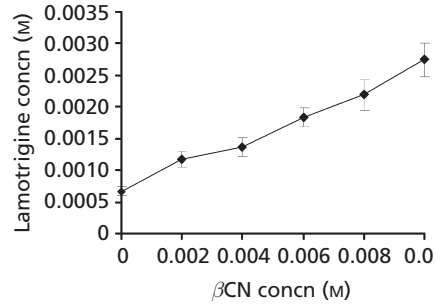

Figure 1 Phase solubility diagram of lamotrigine–βCD system in water. Data are mean ± s.d. (n = 3).

Percentage drug content

Percentage drug content was in the range 96.46 ± 0.71 to 98.28 ± 0.95 for solid dispersions, 95.20 ± 0.88 for βCD physical mixture and 80.25 ± 0.95 for the kneaded product. All determinations are mean ± s.d. of three experiments.

XRD studies

Figure 2 shows the XRD patterns of pure lamotrigine, hydrophilic carriers and their corresponding binary systems with lamotrigine. Lamotrigine (Figure 2A) showed sharp and intense peaks at 28.31°, 26.63°, 28.79°, 12.36°, 26.25° and 17.85° (2θ) with peak intensities of 172, 149, 119, 110, 110 and 81, respectively, indicating its crystalline nature. The XRD pattern of pure βCD is shown in Figure 2B. Crystallinity was determined by comparing representative peak heights in the diffraction patterns of the binary systems with those of a reference. The relative degree of crystallinity (RDC) of lamotrigine in binary systems was calculated according to the equation $RDC = I_{sam} / I_{ref}$, where I_{sam} is the peak height of the sample under investigation and I_{ref} is the peak height at the same angle for the reference with the highest intensity (Ryan 1986). The peak height at 28.79° (2θ) was used for calculating the RDC of the kneaded product and physical mixture. The RDC value of the physical mixture was 0.7394. However, the peak of lamotrigine at the same angle had disappeared in the kneaded product. The crystallinity of lamotrigine was significantly reduced in both the physical mixture (Figure 2C) and the kneaded system (Figure 2D) but to a much greater extent in the latter, as almost all intense peaks of pure lamotrigine had completely disappeared.

In the binary systems of lamotrigine with hydrophilic polymers, the lamotrigine peaks had completely disappeared in all the solid dispersions prepared using PVP K30 (Figure 2F–H). However, some peaks of pure lamotrigine are still visible in solid dispersions prepared with PEG 6000: RDC 0.2848 (1:3) and RDC 0.4197 (1:5) (Figures 2J–L). The absence of

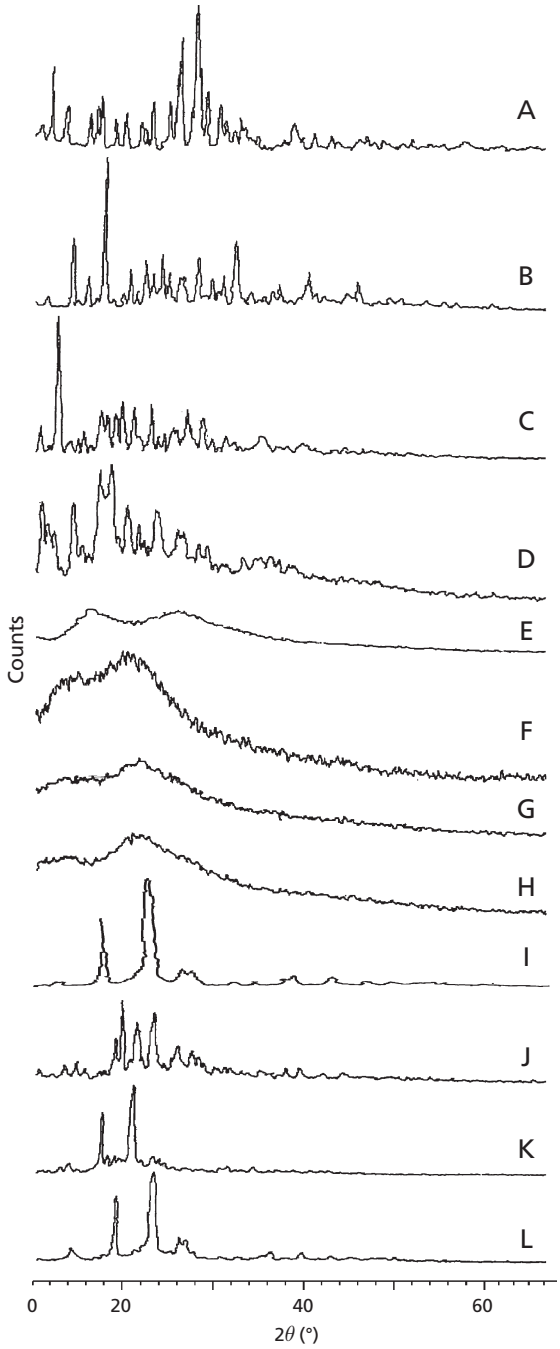

Figure 2 XRD patterns of single components and binary systems of lamotrigine and βCD, PVP K30 and PEG 6000: (A) lamotrigine; (B) βCD; (C) lamotrigine–βCD physical mixture; (D) lamotrigine–βCD inclusion complex; (E) PVP K30; (F) lamotrigine–PVP K30 (1:1) solid dispersion; (G) lamotrigine–PVP K30 (1:3) solid dispersion; (H) lamotrigine–PVP K30 (1:5) solid dispersion; (I) PEG 6000; (J) lamotrigine–PEG 6000 (1:1) solid dispersion; (K) lamotrigine–PEG 6000 (1:3) solid dispersion; (L) lamotrigine–PEG 6000 (1:5) solid dispersion.

peaks indicated that the drug was uniformly dispersed in the carriers. Furthermore, in the kneaded system and solid dispersions with PVP K30, it could be concluded that the drug might have transferred to the amorphous state, as no peaks were visible.

FTIR studies

Figure 3 shows the FTIR spectra of lamotrigine, βCD, physical mixture, inclusion complex and solid dispersions. The IR spectrum of lamotrigine (Figure 3A) is characterized by principal absorption peaks at 3451 cm^{-1} (N–H aromatic); 3212 cm^{-1} (C–H aromatic); 1630 cm^{-1} (C=N); 1292 cm^{-1} (C–N); 1556 cm^{-1} (C=C aromatic); 1052 cm^{-1} (C–Cl); 738 cm^{-1} (*o* substituted benzene); 756, 793 and 805 cm^{-1} (*m* substituted benzene). The IR spectrum of βCD (Figure 3B) shows prominent peaks at 3389 cm^{-1} (O–H); 2924 cm^{-1} (C–H); 1649 cm^{-1} (H–O–H bending); 1157 cm^{-1} (C–O) and 1028 cm^{-1} (C–O–C). The intense peaks in the spectra of lamotrigine and βCD are due to asymmetric stretching vibrations of the functional groups. The IR spectra of the physical mixture (Figure 3C) shows a shift of 1630 cm^{-1} to 1621 cm^{-1} (C=N) and 1556 cm^{-1} to 1557 cm^{-1} (C=C aromatic), with a decrease in the peak intensities. The peak of C–H stretch (3212 cm^{-1} aromatic) of lamotrigine was not visible. All other peaks of lamotrigine were smoothened, indicating strong physical interactions of lamotrigine with βCD. In the

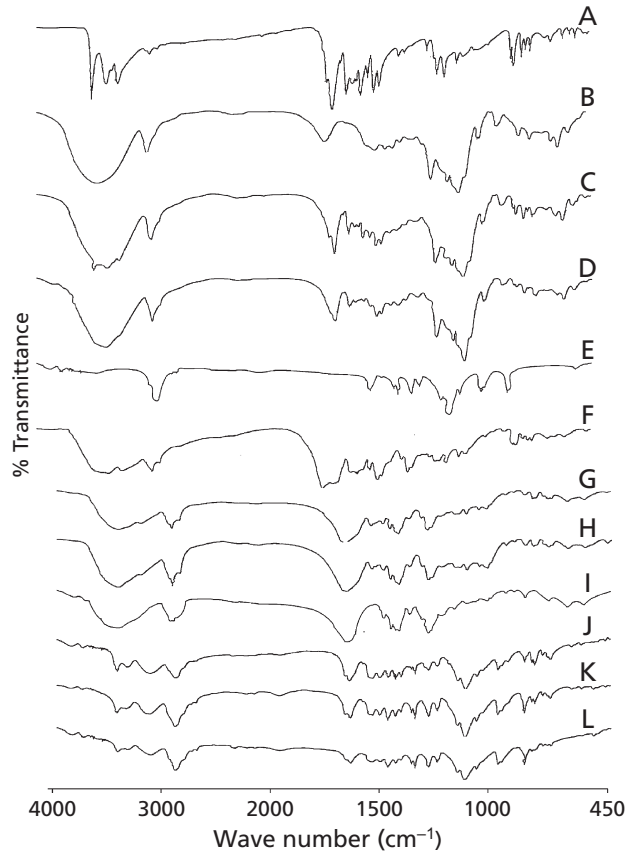

Figure 3 FTIR spectra of single components and binary systems of lamotrigine, βCD, PVP K30 and PEG 6000: (A) lamotrigine; (B) βCD; (C) lamotrigine–βCD physical mixture; (D) lamotrigine–βCD inclusion complex; (E) PVP K30; (F) lamotrigine–PVP K30 (1:1) solid dispersion; (G) lamotrigine–PVP K30 (1:3) solid dispersion; (H) lamotrigine–PVP K30 (1:5) solid dispersion; (I) PEG 6000; (J) lamotrigine–PEG 6000 (1:1) solid dispersion; (K) lamotrigine–PEG 6000 (1:3) solid dispersion; (L) lamotrigine–PEG 6000 (1:5) solid dispersion.

IR spectrum of the inclusion complex (Figure 3D) the peaks of lamotrigine at 3212 cm^{-1} (C–H aromatic), 756, 793 and 805 cm^{-1} (*m* substituted benzene), 738 cm^{-1} (*o* substituted benzene) and 1052 cm^{-1} (C–Cl aromatic) had completely disappeared, indicating that the halogen-substituted aromatic ring of the guest has been entrapped in the hydrophobic cavity of the host molecule. This could also be confirmed by the very low intensity of the peak of the guest at 1557 cm^{-1} (C = C aromatic) in the spectrum from the inclusion complex. Furthermore, the peak of lamotrigine at 3451 cm^{-1} (N–H aromatic) was not visible in the inclusion complex, which might be because of strong hydrogen bonding with the OH group of βCD (Mura et al 1999; Fernandes et al 2002). The peak for the OH group of βCD at 3389 cm^{-1} was shifted towards lower frequency 3338 cm^{-1} due to intermolecular hydrogen bonding with lamotrigine (Figure 3D). The peak at 1649 cm^{-1} in the IR spectrum of βCD due to water of crystallization was also absent from the spectra for the physical mixture and inclusion complex. The binary systems of lamotrigine–βCD did not show any new peaks, indicating that no chemical bonds had formed in the complexes, and indicating formation of inclusion complexes in the solid state.

In the spectra for the solid dispersion systems of lamotrigine–PVP K30 (Figure 3F–H) and lamotrigine–PEG 6000 (Figure 3J–L), the absorption bands of lamotrigine that could be assigned to the free NH_2 and the NH_2 involved in intramolecular hydrogen bonding changed or were absent. This might be a consequence of hydrogen bonding between NH_2 of lamotrigine and nitrogen (N) and C = O of PVP K30, or the lone pairs of the oxygen atom in PEG 6000. The peak for the dichlorosubstituted benzene ring at 805 cm^{-1} was also absent from the solid dispersions. These results suggest intermolecular hydrogen bonding between lamotrigine and PVP or PEG. However, no additional peaks were observed in any of the binary systems, indicating absence of any chemical interaction between lamotrigine and the carriers (Ford 1986; Ruan 2005).

DSC studies

This method was used to identify the inclusion complex of drug with βCD. The DSC thermogram of lamotrigine alone (Figure 4A) shows an endothermic *T*max of 220.16°C, corresponding to the melting point of the crystalline form of lamotrigine. The physical mixture (Figure 4C) shows a very small peak, with decreased peak intensity. For the inclusion complex (Figure 4D), the characteristic melting peak of lamotrigine was lost. The disappearance of the thermal features of the drug indicated that the drug had penetrated into the βCD cavity, replacing the water molecules (Echezarreta-Lopez et al 2000; Fernandes et al 2002). The DSC thermogram of βCD (Figure 4B) showed a broad endothermic peak at 91.78°C, indicating a dehydration process. The peak at 184.37°C indicates irreversible solid–solid phase transition; the final degradation process is shown by the broad peak at 328.66°C (Veiga et al 1998; Giordano et al 2001; Mukne & Nagarsenker 2004; Longxiao & Suyan 2006). For the physical mixture (Figure 4C), the peaks of βCD shifted to 87.23°C and 320.14°C, indicating dehydration and solid–solid phase transition, respectively; in the complex the peaks of βCD shifted to 44.63°C and 317.30°C, indicating similar thermal behaviour.

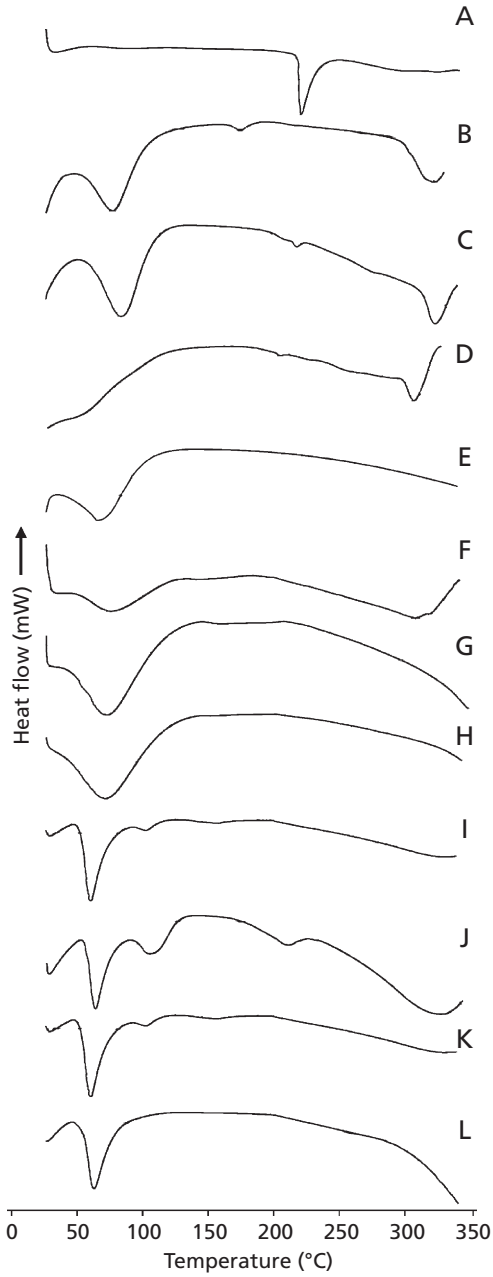

Figure 4 DSC curves of single components and binary systems of lamotrigine and βCD, PVP K30 and PEG 6000: (A) lamotrigine; (B) βCD; (C) lamotrigine–βCD physical mixture; (D) lamotrigine–βCD inclusion complex; (E) PVP K30; (F) lamotrigine–PVP K30 (1:1) solid dispersion; (G) lamotrigine–PVP K30 (1:3) solid dispersion; (H) lamotrigine–PVP K30 (1:5) solid dispersion; (I) PEG 6000; (J) lamotrigine–PEG 6000 (1:1) solid dispersion; (K) lamotrigine–PEG 6000 (1:3) solid dispersion; (L) lamotrigine–PEG 6000 (1:5) solid dispersion.

The DSC thermograms of PVP K30 (Figure 4E) and PEG 6000 (Figure 4I) show sharp endothermic peaks at 71.90°C and 68.49°C, respectively, indicating melting points of the polymers. In the DSC thermograms of solid dispersions of

lamotrigine with PVP K30 (Figure 4F–H), the sharp melting point peak of pure lamotrigine at 220.16°C was not visible. The characteristic features of the lamotrigine peak were lost. This indicated that lamotrigine was molecularly dispersed (Kim et al 2006) and no longer present as a crystalline material, but was converted into the amorphous state (Mooter et al 1998; Ruan et al 2005). Solid dispersions of lamotrigine with PEG 6000 showed similar thermal behaviour as PVP K30 in the ratios 1:3 and 1:5 (Figures 4K and 4L). The absence of lamotrigine peaks suggested that lamotrigine was completely soluble in the liquid phase of PEG 6000 (Mooter et al 1998; Damian et al 2000; Ruan et al 2005).

Saturation solubility studies

The binary systems of lamotrigine showed enhanced solubility compared with pure drug. The percentage increases in the aqueous solubility of lamotrigine are shown in Table 1. The 1:1 inclusion complex of lamotrigine with βCD showed higher solubility than pure drug alone ($P < 0.05$). This significant enhancement in solubility of the complex is mainly attributed to the formation of stable inclusion complexes of lamotrigine with βCD. The stability constant ($369.96 \pm 2.26\ \text{M}^{-1}$) suggests that lamotrigine and βCD have sufficient affinity towards each other to form a stable inclusion complex, as the solubility of complex was found to be increased by 205.04%. The physical mixture also had higher solubility than the pure drug (not significant). Furthermore, no significant difference was found between the solubility of lamotrigine from the physical mixture and the inclusion complex. The enhancement in aqueous solubility of lamotrigine can be explained in terms of wetting property and hydrophilicity of βCD, with simultaneous reduction in the crystallinity of the drug caused by the kneading process and inclusion into the hydrophobic cavity of the βCD (Szetli 1994; Uekama & Hirayama 1996; Trapani et al 2000).

All solid dispersion systems displayed higher solubility of lamotrigine than pure drug. However, the enhancement in solubility of solid dispersions was not statistically significant when compared with pure lamotrigine, except for PVP K30 (1:5) solid dispersion. The 1:5 drug:carrier ratio was more soluble than the 1:1 and 1:3 ratios in solid dispersions of PVP K30 and PEG 6000. The aqueous solubility of lamotrigine in solid dispersion with PVP K30 (1:5) was increased by 7.35 fold ($P < 0.01$). Higher hydrophilicity and the surface properties of PVP K30 may contribute to the increased aqueous solubility of drugs. PVP K30 performed better in this respect than PEG 6000. Enhancement in solubility was observed in the following order: PVP K30 > βCD > PEG 6000. However, the differences in the solubility of lamotrigine in these hydrophilic carriers were not statistically significant.

Table 1 Solubility data for lamotrigine, physical mixtures of lamotrigine–βCD, inclusion complex and solid dispersions (SD)

	Solubility in water (mg mL^{-1})[a]	s.e.m.	% increase in solubility
Lamotrigine	172 ± 1.0	0.58	–
βCD physical mixture	427 ± 1.7	1.00	148.25
βCD kneaded inclusion complex	524.67 ± 1.5*	0.88	205.04
Lamotrigine–PVP K30 (1:1) SD	419.33 ± 1.5	0.87	143.79
Lamotrigine–PVP K30 (1:3) SD	586.33 ± 1.5	0.87	240.88
Lamotrigine–PVP K30 (1:5) SD	1265 ± 1.0**	0.57	635.46
Lamotrigine–PEG 6000 (1:1) SD	183 ± 1.0	0.58	06.39
Lamotrigine–PEG 6000 (1:3) SD	206.67 ± 1.5	0.87	19.76
Lamotrigine–PEG 6000 (1:5) SD	288.33 ± 1.5	0.88	67.63

[a]at 25°C (mean ± s.d., n = 3)
*$P < 0.05$, **$P < 0.01$ vs pure lamotrigine.

Dissolution studies

The dissolution curves of lamotrigine, physical mixture, inclusion complex and solid dispersions in 0.1M HCl at 37 ± 0.5°C are shown in Figure 5.

It is evident that the inclusion complex and solid dispersions improved the dissolution rate of lamotrigine to the greatest extent. Table 2 shows the percentage drug dissolved in 15 min (DP_{15}) for lamotrigine and its binary systems with hydrophilic carriers. According to these results, all binary systems of lamotrigine have better dissolution rates than the pure drug. The kneaded product had the highest dissolution rate compared with the pure drug ($P < 0.05$), indicating complete release of lamotrigine from the complex. This behaviour might be attributed to the highly energetic amorphous state and inclusion complex formation (Loftsson & Brewster 1996). The physical mixture also showed an improved dissolution rate compared with lamotrigine but this was not statistically significant. Furthermore, no significant differences

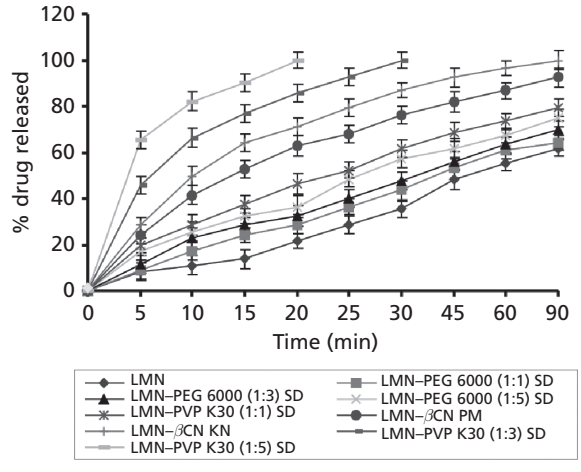

Figure 5 Dissolution curves of lamotrigine (LMN) alone and from binary systems of lamotrigine with βCD, PVP K30 and PEG 6000. SD, solid dispersion; PM, physical mixture; KN, kneaded product (inclusion complex). Data are mean ± s.d. (n = 3).

Table 2 The dissolution time of pure lamotrigine, lamotrigine–βCD physical mixture, inclusion complex and solid dispersions (SD) in 0.1 M HCl at 37 ± 0.5°C

Sample source	DP_{15}[a]
Lamotrigine	13.8 ± 4.1
βCD physical mixture	52.6 ± 3.9
βCD kneaded inclusion complex	64.1 ± 3.7**
Lamotrigine–PEG 6000 (1:1) SD	24.2 ± 3.2
Lamotrigine–PEG 6000 (1:3) SD	28.6 ± 3.1
Lamotrigine–PEG 6000 (1:5) SD	32.6 ± 3.2
Lamotrigine–PVP K30 (1:1) SD	37.4 ± 3.6
Lamotrigine–PVP K30 (1:3) SD	77.1 ± 3.8
lamotrigine–PVP K30 (1:5) SD	90.2 ± 3.6**

[a]% dissolved at 15 min; mean ± s.d. (n = 3).
**$P < 0.01$ vs pure lamotrigine.

were found between the dissolution rate of lamotrigine from the physical mixture compared with the kneaded system. The increase in dissolution rate for the physical mixture was possibly due to a local solubilization action operating in the microenvironment or to the hydrodynamic layer surrounding the drug particles in the early stages of the dissolution process; enhanced dissolution from the inclusion complex is due to greater hydrophilicity, higher wetting effect and mechanical treatment, which increased the contact between the drug and the carrier and the ability to form a stable inclusion complex of βCD.

In solid dispersion systems, the 1:5 ratio of PVP K30 significantly improved the dissolution rate of lamotrigine by a greater extent than any other solid dispersion systems ($P < 0.01$). Increase in the weight fraction of the polymer gave more rapid dissolution (Corrigan et al 1985). The other solid dispersion systems of lamotrigine also showed enhanced dissolution of lamotrigine, although this was not statistically significant compared with pure lamotrigine. Also, no significant differences in the dissolution rates of lamotrigine were found when all the solid dispersion systems were compared statistically. The rapid dissolution of lamotrigine from solid dispersions may be attributed to a decrease in the crystallinity of drug and its molecular and colloidal dispersion in the hydrophilic carrier matrix. As the soluble carrier dissolves, the insoluble drug gets exposed to dissolution medium in the form of very fine particles for quick dissolution (Geneidi et al 1978; Save & Venkitachalam 1992). The enhancement in drug dissolution from the lamotrigine–PVP K30 (1:5) solid dispersion systems was higher than from the all other binary systems of PVP K30, βCD and PEG 6000, showing the importance of the proper choice of carrier. The order of efficiency of carriers (based on DP_{15} values) is: PVP K30 > βCD > PEG 6000. However, the differences in the dissolution rates of lamotrigine from these hydrophilic carriers were not statistically significant. The higher dissolution rate of lamotrigine from PVP solid dispersion systems may be accredited to the greater amorphizing properties of PVP compared with PEG, as reported in an earlier papers (Cirri et al 2004) and the prevention of nucleation (Gupta et al 2004). Furthermore, it is clear from XRD studies that the recrystallization of lamotrigine was suppressed by PVP in solid dispersion systems, which is known as an inhibitor of drug recrystallization (Sekikawa et al 1978; Yagi et al 1996).

Other factors that might contribute to enhancement of the dissolution rate are greater hydrophilicity and surfactant property of polymers, increased wettability and dispersibility, and reduction in the particle size of the drug (Ford 1986). The greater hydrophilicity and surfactant property of polymers results in greater wetting and increases the surface available for dissolution, by reducing interfacial tension between the hydrophobic drug and the dissolution medium. During dissolution experiments, it was noticed that drug carrier systems sank immediately, whereas pure drug floated on the surface of the dissolution medium for a longer period of time.

Conclusions

In the binary systems of lamotrigine prepared with different hydrophilic carriers, βCD and PVP K30 showed superior performance over PEG 6000 in enhancing aqueous solubility and the dissolution of lamotrigine. The improved dissolution rate by βCD was due to an increase in solubility, brought about by complexation. Among the carriers used, PVP K30 is an appropriate choice to enhance the aqueous solubility and dissolution. XRD, FTIR and DSC studies of the binary systems of lamotrigine with βCD, PVP K30 and PEG 6000 showed that the crystallinity of lamotrigine was decreased to a greater extent in the complex, as well as in solid dispersions, which markedly increased the dissolution rate of lamotrigine. Based on the results, solid dosage forms containing lamotrigine for oral administration could be manufactured with βCD, PVP K30 or PEG 6000, providing higher dissolution rate and faster onset of action, improving bioavailability. Further studies are required to determine whether bioavailability is improved in-vivo.

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