

In vitro and *in vivo* evaluation of fast-dissolving tablets containing solid dispersion of lamotrigine

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Abstract

Aim: Investigation of *in vitro/in vivo* behavior of fast-dissolving tablets containing solid dispersions (SDs) of lamotrigine (LM) was the aim and focus of the present research work. **Material and Methods:** The effect of various hydrophilic polymers on the aqueous solubility of LM was studied. Polyethylene glycol (PEG 6000) was selected as the vehicle and SDs were prepared by melting and solvent evaporation method (SEM). Evaluation of SD for dissolution indicated SVM was more appropriate as seen from an enhancement in drug dissolution. Infrared spectroscopy, differential scanning calorimetry, and powder X-ray diffraction studies indicated a lack of physicochemical interaction between the drug and the carrier. A total of nine formulations were compressed into fast-dissolving tablets using Avicel pH 102 as a directly compressible filler and ac-di-sol, sodium starch glycolate and croscopovidone as super disintegrates and evaluated for pre- and post-compression parameters and *in vitro* drug release. **Results:** Mathematical analysis of *in vitro* data suggested that first order was most suitable mathematical model for describing the optimized formulation. Stability studies indicated that the effect of storage was insignificant at 5% level of confidence. *In vivo* studies of pure drug, selected formulation and marketed product were carried out in male Wistar rats and pharmacokinetic (PK) parameters were calculated using PK function for Microsoft Excel. The best formulation has shown T_{max} of 0.5 h which was highly significant ($P < 0.05$) when compared with pure drug and marketed formulation. The statistical significance was assessed by one way analysis of variance. **Conclusion:** Therefore, the SDs prepared by SEM using PEG 6000 as hydrophilic carrier can be successfully used for improvement of dissolution of LM and resulted in faster onset of action as indicated by *in vivo* studies.

Key words: Dissolution profile, hydrophilic carrier, solid dispersion, solubility, solvent evaporation method

INTRODUCTION

Lamotrigine (LM) is an anticonvulsant drug used in the treatment of epilepsy and bipolar disorder.^[1] Chemically unrelated to other anticonvulsants (due to LM being a phenyltriazine), LM has relatively few side-effects and does not require blood monitoring in monotherapy. LM also acts as a mood stabilizer.^[2] LM 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 Biopharmaceutics Classification System). Peak plasma concentrations occur anywhere from 1.4 to 4.8 h following drug administration. 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. This may result in the delayed onset of action because of sub-therapeutic plasma drug levels and may also lead to therapeutic failure.

Solid dispersions (SDs)^[3,4] refer to a system in which hydrophobic drug is dispersed in a hydrophilic matrix, in order to improve its dissolution properties and bioavailability. In SD, a drug can exist in an amorphous or crystalline form in hydrophilic polymeric carriers^[5,6] such as polyethylene glycols (PEG), polyvinyl pyrrolidone K30 (PVP K30), urea, etc., which results in improved solubility and dissolution rates.

The objective of the present research work was to formulate SDs of LM; two hydrophilic carriers were evaluated to determine their effect on solubility of LM; different methods were then evaluated to select the best method of preparation

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of SDs. Furthermore, the SDs were formulated into fast-dissolving tablets and effect of formulation on the T_{max} of LM was studied.

MATERIALS AND METHODS

Materials

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

Methods

Screening of appropriate carrier for LM SD using solubility studies

Solubility measurements were performed according to method reported by Higuchi and Connors.^[7] 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 the drug was added to each flask. The contents of each flask (10 ml) were equilibrated by shaking for 48 h in a thermostatically controlled water bath at $37^{\circ}\text{C} \pm 0.1^{\circ}\text{C}$. After 48 h, samples were analyzed at 304 nm for LM. Solubility studies were performed in triplicate ($N = 3$).

Preparation of physical mixtures and SDs

For LM, the physical mixtures and SDs were prepared in three different ratios by using PEG 6000 as a hydrophilic carrier. The drug to carrier ratio is shown in Table 1. PEG 6000 was chosen as it was found to give a better dissolution profile with that of LM.

Preparation of physical mixture by trituration method

The physical mixtures of PEG 6000 and the drugs were prepared by triturating the required quantity of drug and PEG 6000 for 5 min in a glass container, sieved and stored in desiccators for further estimation.

Preparation of SDs by melting method

PEG 6000 was melted in a beaker on a water bath maintained at $50\text{--}60^{\circ}\text{C}$. Required amount of the 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.

Preparation of SDs by solvent evaporation method (SEM)

Accurately weighed quantity of PEG 6000 was dissolved in 10 ml of acetone. To these solutions, accurately weighed quantities of the drug was added and allowed to dissolve. The solution was transferred to a petri dish and the solvent was allowed to evaporate at room temperature for 1 h and then was kept in desiccators for 48 h. SDs thus obtained were crushed, pulverized, sifted and stored in desiccators for further evaluation.

Dissolution studies

The physical mixture and 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)^[8] temperature $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ and paddles rotated at 50 rpm. Samples of 150 mg of pure drug, physical mixture and SD samples equivalent to 150 mg of drug [Table 1] were filled inside muslin cloth pouches and dropped inside 900 ml of dissolution medium. A volume of 10 ml of samples were withdrawn every 10 min, filtered through a membrane filter (pore size $0.45\text{ }\mu\text{m}$) and analyzed at 304 nm for LM. Dissolution studies were done in triplicate ($N = 3$) and calculated mean values of cumulative drug release were used while plotting the drug release curves. Based on the above studies, the formulation SD1 was selected for further studies.

Characterization of SDs of LM^[9]

Fourier transforms infrared spectroscopy (FTIR)

Fourier transform infrared spectra were obtained using Thermo Nicolet 380 FTIR. The scanning range was $40\text{--}4000/\text{cm}$ and the resolution was $4/\text{cm}$.

Differential scanning calorimetry (DSC)

The DSC thermograms of samples (LM, PEG, LM – PEG 6000 SDs) were recorded on a DSC (SISI Nanotech). The samples (6.5–10 mg) were heated under nitrogen atmosphere in hermetically sealed aluminum pans over a temperature range 20°C to 350°C at a constant rate of $20^{\circ}\text{C}/\text{min}$ under nitrogen purge (10 ml/min).

Powder X-ray diffraction (PXRD)

The PXRD patterns were determined for LM by Panalytical's X'Pert Pro for PEG and LM — PEG 6000 SDs. The scanning rate was $1^{\circ}/\text{min}$ over a 2θ range of $1\text{--}50^{\circ}\text{C}$.

Formulation of fast-dissolving tablets

The SD having the maximum solubility and dissolution rate (SD1) was selected and 25 mg LM equivalent was incorporated into each formulation. Directly compressible filler chosen for the formulations were Avicel pH 102 (36–39%) and the super disintegrates chosen were ac-di-sol (1–3%), sodium starch glycolate (4–6%) and crospovidone (2–4%). Magnesium Stearate (0.5–1%) was selected for its lubricant and anti-adherent

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

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

PEG: Polyethylene glycol; SD: Solid dispersion

properties and Aerosil (0.5-1%) as a glidant. Aspartame (4-4.5%) imparted a sweet taste to the formulations.

All the ingredients as depicted in Table 2 (except magnesium stearate) were mixed homogenously and co-ground in a mortar and pestle. Finally, magnesium stearate was added and mixed for 5 min. A total of nine formulations were prepared according to Table 2 and the powder blend was evaluated for flow properties such as tapped density, bulk density, Hausner ratio, compressibility index and angle of repose.

Compression and evaluation of tablets

The tablet weight was adjusted to ~100 mg. Fast-dissolving tablets of LM were formulated. The mixed blend of drug and excipients was compressed using Cadmach 16 station tablet punching machine to produce flat faced tablets weighing 100 mg each for LM, a minimum of 50 tablets were prepared for each batch and evaluated for parameters such as hardness,^[10] friability,^[11] disintegration time,^[12] wetting time,^[13] weight variation,^[14] content uniformity,^[15] and water absorption ratio.^[16]

Dissolution studies of prepared formulations

The pure drug, physical mixture, prepared tablet, and the marketed formulation were then subjected to dissolution studies using USP Paddle Type II apparatus. The dissolution medium used was stimulatory salivary solution (pH 6.6).^[17] A volume of 10 ml of samples were withdrawn after every 1 min and analyzed at 304 nm for LM. Dissolution studies were done in triplicate ($N = 3$) and cumulative drug release with standard deviations were reported. On the basis of dissolution studies formulation F1 showing 97% drug release was selected as the best formulation.

Mathematical analysis of in vitro data

The release data of optimized formulation was examined according to the zero-order, first-order, and Higuchi's and Korsmeyer-Peppas model.^[18] It was observed that the first order was most suitable mathematical model for describing the optimized formulation.

Stability studies

Accelerated stability studies were performed according to International Conference on Harmonization (ICH) guidelines at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$, $75\% \pm 5\%$ relative humidity (RH) for 6 months

period. Tablets containing optimized formulation F1 were removed at the end of 3 and 6 months and evaluated for hardness, and disintegration time and drug release. Tests were repeated 3 times ($N = 3$) at each time interval and mean values reported with a standard deviation. A paired *t*-test was applied to tablet dissolution initial and after 6 months results in order to study the effect of storage.

In vivo studies

The bioavailability studies for pure LM, optimized formulation of LM (F1), and Marketed Formulation (Lamitor DT[®]) were carried out using male Wistar rats (200-250 g). The animals were maintained in a clean room at a temperature between $20^{\circ}\text{C} \pm 25^{\circ}\text{C}$ with 12-h light and dark cycles and controlled RH. The animals were fasted for 12 h prior to commencement of the study as well as during the study and had access to water *ad libitum*. The institutional animal ethical clearance (vide letter no. CPCSEA/MRCP/2008/1217) was obtained before conducting the studies. They were divided into four groups (six in each group); Group I served as a control group, whereas other three groups were treated with pure drug (suspended in normal saline with the help of Tween 80),^[19] tablet formulation containing SD of LM (F1) and Marketed Formulation respectively. Tablets with a dose of 10 mg/kg body weight of rats were administered by dispersing in distilled water through oral feeding pipe.

Blood samples were collected through the lateral tail vein of rats at 10, 20, 30 min followed by 1, 1.5, 2, 3, 4, 6, and 24 h after dosing. The blood samples were centrifuged at 3000 rpm for 10 min and 100 μl of plasma samples were stored at -20°C until analysis.

The plasma concentration of the drug was determined by high performance liquid chromatography (HPLC).^[20] The HPLC system consisted of a system controller (M-721), a data module (M-730), a solvent delivery pump (M-501), an auto sampler (WISP-712) and a variable wavelength ultraviolet detector (M-481). Chromatographic separations were performed using symmetry C₁₈ stainless steel column (150 mm $\times$ 3.9 mm inner diameter, 5 μm). A mobile phase consisting of 0.01 M potassium phosphate–acetonitrile–methanol (70:20:10% v/v/v) at a pH adjusted to 6.7 was used using a flow rate of 1.3 ml/min and monitored at 214 nm with a sensitivity of 0.01 absorbance units full scale and a chart speed of 0.5 cm/min.

The results obtained were analyzed for various non-compartmental pharmacokinetic (PK) parameters using PK functions. Furthermore, the PK data were analyzed statistically by one way analysis of variance (ANOVA) followed by Dunnett *post hoc* test for multiple comparison.

Statistical analysis

The results of biochemical estimations are reported as mean $\pm$ standard error. The total variation present in data was analyzed by one-way ANOVA. Differences among the means were analyzed by Scheffe's test. For this, a window based SPSS computer package was used.

Table 2: Formulation of fast-dissolving tablets of Lamotrigine

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Amount of complex (SD1) equivalent to 25 mg of Lamotrigine (1:1)	50	50	50	50	50	50	50	50	50
Avicel PH 102	39	37	36	39	37	36	39	37	36
Ac-di-sol	3	1	0	3	1	0	3	1	0
Sodium starch glycolate	0	6	4	0	6	4	0	6	4
Crospovidone	2	0	4	2	0	4	2	0	4
Magnesium stearate	1	0.5	0.75	0.5	0.75	1	0.75	1	0.5
Aerosil	0.5	1	0.75	1	0.75	0.5	0.75	0.5	1
Aspartame	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5

RESULTS

Screening of appropriate carrier for LM SD using solubility studies

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 LM as compared to PEG 4000. The aqueous solubility of LM 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 as compared to pure drug. This may be attributed to more number of ether linkages in case of PEG 6000 and hence greater solubility.

Comparative dissolution data LM

Both physical mixtures and SDs showed enhanced dissolution rate as compared to pure drug. SD increased the solubility and maximized 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 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 the molecular level, and expansion of the surface area for dissolution. LM when combined with PEG 6000 in 1:2 or 1:5 ratio did not give satisfactory drug release. Maximum drug release was seen when LM was combined with PEG 6000 in 1:1 ratio for SD prepared by the SEM (As depicted in Figure 2).

Drug excipient interaction studies

FTIR

The spectrum of LM 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 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 infrared spectroscopy (IR) spectra of pure drug (LM) and its SD revealed that all the major peaks of the pure drug and PEG 6000 appeared with negligible variation in the IR spectrum of the SD, indicating that there was no chemical interaction between the drug and polymer [Figures 3 and 4]. From this, it can be concluded that the drug has maintained its characteristic properties in the SDs prepared by both methods.

DSC

The DSC curve of pure drug LM 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 (As elucidated in Tables 5 and 6).

In both melting and SEMs, both drug as well as the polymer did show a slight shift in the peaks indicating amorphization of the drug

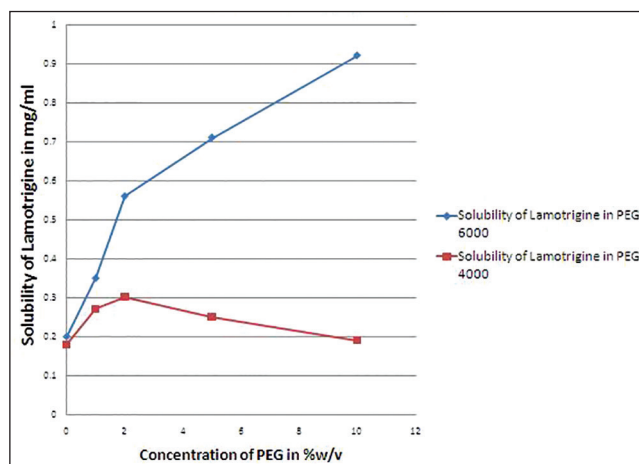


Figure 1: Effect of carriers on the solubility of pure lamotrigine

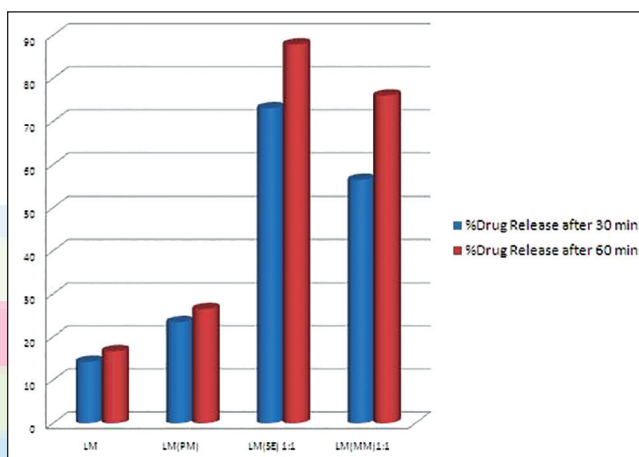


Figure 2: Comparative dissolution data lamotrigine. LM: Lamotrigine, PM: Physical mixture, SE: Solvent evaporation method, MM: Melting method

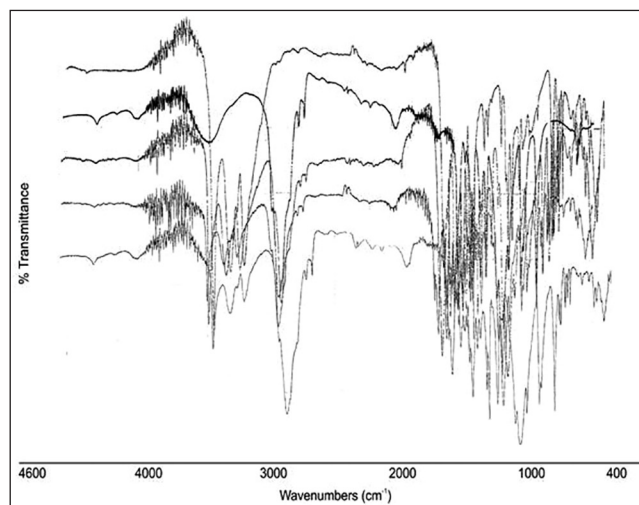


Figure 3: Fourier transforms infrared spectroscopy curves melting method (a) pure drug lamotrigine (b) polyethylene glycol (c) solid dispersion (SD) 1:1 (d) SD 1:2 (e) SD 1:5

in the polymer however more pronounced results were elucidated in SEM. The endothermic thermogram of the pure drug in the formulation has slightly changed its shape and become bit broad in the formulation. Perhaps, it could be due to reason that the pure drug must have become more amorphous in the formulation, which may be helpful in increasing the solubility of pure drug in the formulation.

X-ray powder diffraction

The solid state crystallinity of LM, PEG 6000 and formulations prepared by melting and SEM, were studied by PXRD technique [Figures 5-8]. The reduction in crystallinity of LM in the formulations was observed and it was also noted that the crystallinity was decreased with an increase in concentration of PEG 6000 (1:1, 1:2, 1:5)

Evaluation of pre-compression parameters

The pre-compression characteristics of all the nine formulations of LM indicated that the tapped density, bulk densities, Hausner's

ratio, compressibility index and angle of repose for all the formulations was within the acceptable range [Table 3].

Evaluation of LM tablets

All the tablet parameters were measured 6 times and the mean reported with standard deviations. The prepared tablets were spherical and white in color. The mean weight, content uniformity and friability of all the nine formulations were within the acceptable range. The hardness range for the fast-dissolving tablets should be between 2 and 4 kg/cm² and for all the LM formulations the hardness range was found to be between 3.3 and 3.8. Fast-dissolving tablets are required to disintegrate within 2 min and tablets from all the batches were found to disintegrate within 63-67 s. The wetting time for the tablets is used as an indicator of the ease of tablet dissolution in the buccal cavity. Hydrophobicity of the compound as well as inner composition of the tablet has an effect on the wetting time of the tablet. Wetting time for all the formulations was ranging between 31 and 35 s

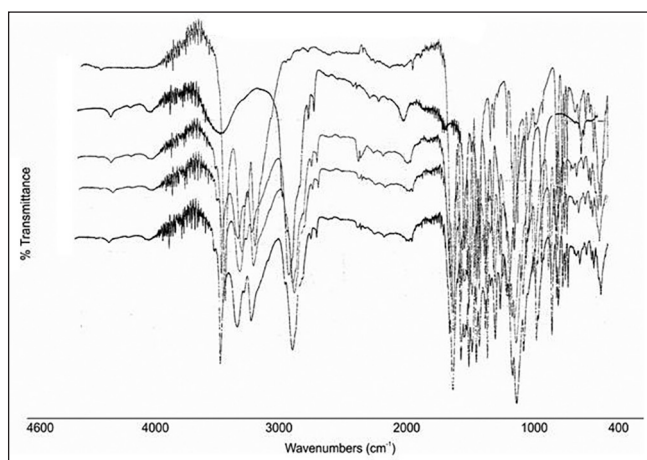


Figure 4: Fourier transforms infrared spectroscopy curves solvent evaporation method (a) pure drug lamotrigine (b) polyethylene glycol (c) solid dispersion (SD) 1:1 (d) SD 1:2 (e) SD 1:5

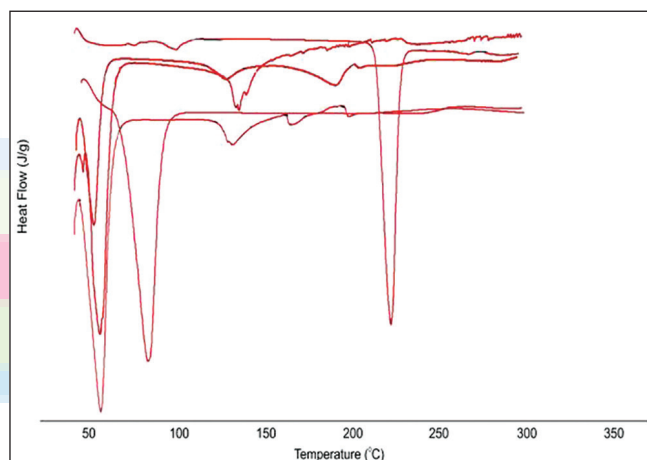


Figure 5: Differential scanning calorimetry thermogram melting method (a) pure drug lamotrigine (b) polyethylene glycol (c) solid dispersion (SD) 1:1 (d) SD 1:2 (e) SD 1:5

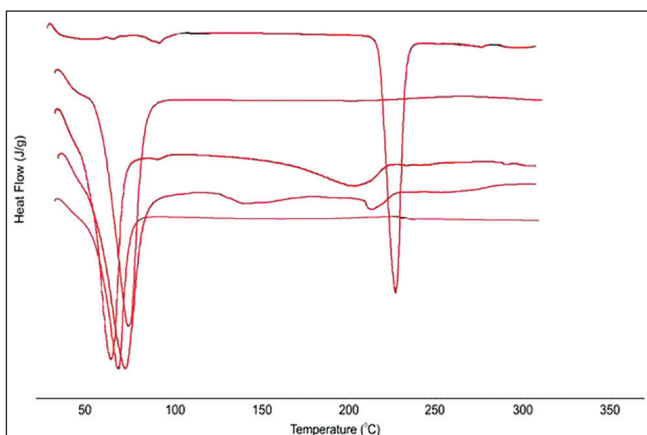


Figure 6: Differential scanning calorimetry thermogram solvent evaporation method (a) pure drug lamotrigine (b) polyethylene glycol (c) solid dispersion (SD) 1:1 (d) SD 1:2 (e) SD 1:5

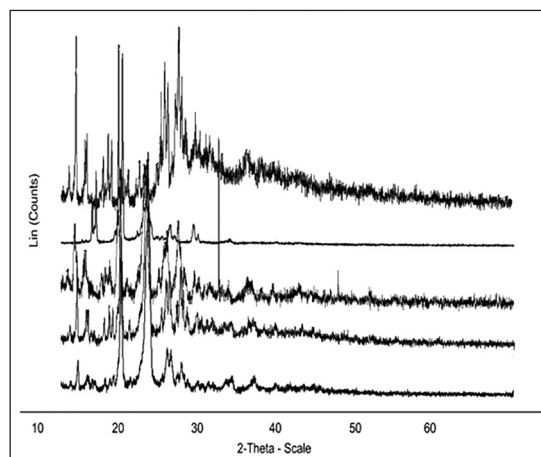


Figure 7: Powder X-ray diffraction melting method (a) pure drug lamotrigine (b) polyethylene glycol (c) solid dispersion (SD) 1:1 (d) SD 1:2 (e) SD 1:5

the lowest being for Formulation F1 containing ac-di-sol and crospovidone combination. Ac-di-sol has a rapid and swelling action, whereas crospovidone is known to cause water wicking and swelling within the tablet. Both these attributes cause faster water ingress within the tablet thus lowering the wetting time. Water absorption ratio which is the ratio of the weights of the tablet after and before the water absorption was in a range of 51-52 s [Table 4].

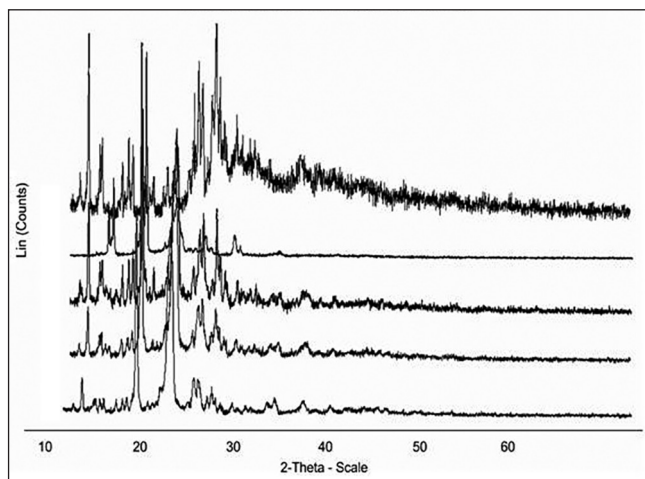


Figure 8: Powder X-ray diffraction solvent evaporation method (a) pure drug lamotrigine (b) polyethylene glycol (c) solid dispersion (SD) 1:1 (d) SD 1:2 (e) SD 1:5

Dissolution studies of prepared formulation

From the dissolution analysis, it was clear that the maximum percentage of drug release was observed with the formulation F1 containing ac-di-sol (crosscarmillose Sodium) and crospovidone (cross-linked polyvinyl pyrrolidone) combination for LM. The increase in dissolution from formulation containing ac-di-sol and crospovidone may be due to the wetting and solubilizing effect of these superdisintegrants which could reduce the interfacial tension between LM and the dissolution medium. All the formulations showed enhanced dissolution rate as compared to pure LM and marketed product. (Figure 9)

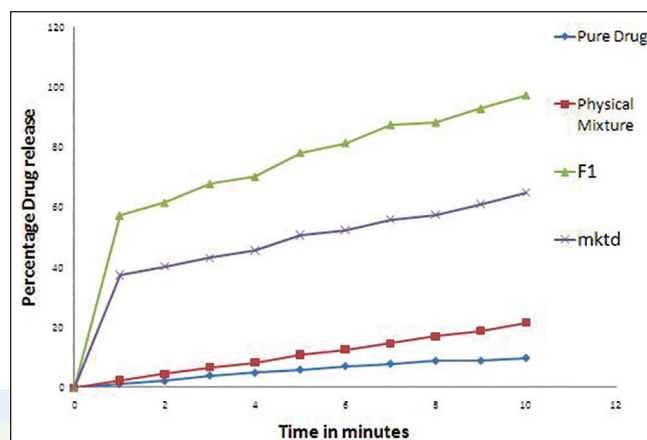


Figure 9: Drug release profile of lamotrigine, physical mixture, formulation containing solid dispersion and marketed product

Table 3: Powder characteristics of Lamotrigine

Formulation	Tapped density g/cm ³ (T) N = 6 ± SD	Bulk density g/cm ³ (B) N = 6 ± SD	Hausner's ratio H = T/B N = 6 ± SD	Carr's index C = 100 (1-1/H)* N = 6 ± SD	Angle of repose (Θ) Tan ⁻¹ = h/r. N = 6 ± SD
F1	0.45±0.03	0.40±0.03	1.13±0.02	12±0.02	26±2
F2	0.47±0.02	0.41±0.04	1.15±0.02	13±0.01	28±3
F3	0.47±0.01	0.39±0.03	1.21±0.03	17±0.03	30±3
F4	0.42±0.03	0.36±0.01	1.17±0.02	15±0.04	29±2
F5	0.40±0.02	0.32±0.02	1.25±0.04	20±0.02	32±1
F6	0.47±0.01	0.40±0.01	1.18±0.01	15±0.01	27±2
F7	0.40±0.04	0.33±0.00	1.21±0.03	17±0.03	31±4
F8	0.42±0.03	0.33±0.06	1.27±0.04	21±0.02	28±1
F9	0.42±0.05	0.36±0.04	1.17±0.01	15±0.02	32±2

Values are expressed as mean±SEM. SEM: Standard error of mean; SD: Solid dispersion

Table 4: Evaluation of Lamotrigine tablets

Sr.no.	Weight variation (mg) N = 6 mean ± SD	Content uniformity (%) N = 6 mean ± SD	Hardness (kg/cm ²) N = 6 mean ± SD	Friability (%) N = 6 mean ± SD	Disintegration time (s) N = 6 mean ± SD	Wetting time (s) N = 6 mean ± SD	Water absorption ratio N = 6 mean ± SD
F1	100±0.2	99.1±0.4	3.5±0.2	0.64±0.2	65±0.2	31±0.1	51.18±0.67
F2	100±0.1	93.2±1.6	3.7±0.4	0.62±0.6	64±0.3	34±0.33	52.00±0.55
F3	100±0.2	97.4±2.1	3.6±0.3	0.60±0.7	64±0.2	35±0.88	51.99±0.45
F4	100±0.3	94.3±2.4	3.5±0.1	0.66±0.1	65±0.2	34±0.51	52.00±0.45
F5	100±0.2	96.1±2.31	3.7±0.6	0.63±0.3	67±0.1	35±0.7	51.97±0.65
F6	100±0.2	95.1±1.31	3.8±0.2	0.67±0.6	65±0.2	35±0.8	51.92±0.34
F7	100±0.1	94.3±1.1	3.4±0.6	0.68±0.8	64±0.3	34±0.73	52.00±0.68
F8	100±0.3	95.5±1.9	3.3±0.8	0.64±0.4	63±0.1	34±0.5	52.00±0.35
F9	100±0.2	99.1±0.1	3.5±0.4	0.62±0.3	65±0.2	34±3.51	52.06±0.5

Values are expressed as mean±SEM. SEM: Standard error of mean; SD: Solid dispersion

Mathematical analysis of *in vitro* dissolution of prepared formulations [Table 5]

The first-order plots were found to be fairly linear for optimized formulation as indicated by their high regression values. Korsmeyer peppas $N < 0.5$ for all the formulations suggest that the release of LM from fast-dissolving tablets followed fickian diffusion mechanism.

Stability studies

It was evident from the paired *t*-test result of LM tablets that the effect of storage was insignificant at 5% level of F {*t* stat (0.0128) < *t* critical (2.3060)} and it can be conclusively stated that the dissolution studies show compliance with the ICH guidelines demonstrating shelf life through curve fitting at 95% confidence limit [Table 6].

In vivo studies for LM

The linear regression analysis of LM [Table 7] was constructed by plotting the peak–area ratio of drug versus analyte concentration (mcg/ml) in spiked plasma samples. The average regression equation and correlation coefficients were calculated. $r^2 = 0.999$ for LM showed good linear relationship between the under peak areas and the concentrations. The lower limit of quantization was 0.05 mcg/ml for determination of LM in plasma. The limit had been sufficient for PK studies of LM.

From the pharmacokinetic analysis, it can be concluded that the *in vivo* studies mimic the *in vitro* results. *In vitro* results demonstrated considerable difference in the percentage drug release between pure drug and Optimized formulation, similarly differences were observed in C_{max} , T_{max} and AUC_{0-t} between pure drug and optimized formulations [Figure 10].

The average peak plasma concentration obtained for the drug [Table 8] and fast-dissolving tablet, indicated an increase in the extent of absorption (AUC_{0-t}). The decrease in the T_{max} values indicated faster absorption from the optimized formulation and increase in the C_{max} values indicated higher attainable plasma drug concentrations with the same dose of the drug. The higher values of PK parameters (AUC_{0-t} , C_{max} , T_{max} and $t_{1/2}$) showed enhancement in bioavailability of LM by formulating fast-dissolving tablet.

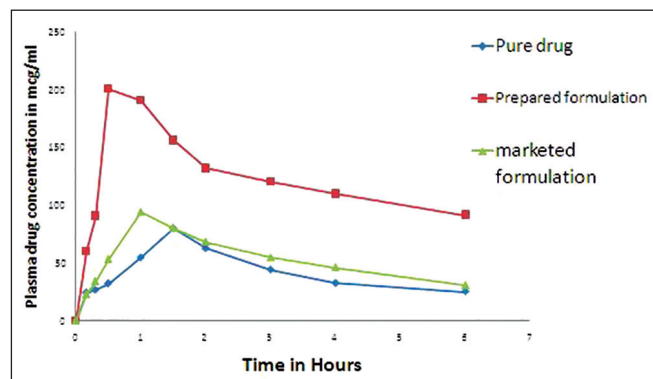


Figure 10: Plasma concentration versus time graphs for lamotrigine

CONCLUSION

The study showed that the dissolution rate of LM was enhanced to a greater extent by SD technique using SEM. PEG 6000 showed most prominent results indicating the usage of this carrier for SD of LM which was comparable to that of the previous works on LM by using PVP K30 (1:5),^[21] which did

Table 5: Fit of different kinetic models for release of Lamotrigine from fast-dissolving tablet

Kinetics model	R^2	K
Zero order	0.7251	6.9166 (mg/min)
First order	0.9173	$0.1251 (\text{min}^{-1})$
Higuchi model	0.9175	27.041
	r^2	n
Korsmeyer peppas model	0.9547	0.2391

Table 6: Accelerated stability studies on Lamotrigine

Parameter N = 6 (mean ± SD)	Initial	3 months	6 months
Weight of tablet (mg)	100±0.1	100±0.3	100±0.4
Hardness (kg/cm ²)	3.5±0.00	3.5±0.2	3.6±0.1
Friability (%)	0.64±0.1	0.64±0.3	0.64±0.2
Wetting time (s)	31.12±3	31.13±2	31.12±5
Content uniformity (%)	99.80±0.1	99.82±0.1	99.80±0.2
Disintegration (s)	64±1	65±3	65.4±4

Values are expressed as mean ± SEM. SEM: Standard error of mean; SD: Solid dispersion

Table 7: *In vitro* cumulative percentage drug release at 40±2°C, 75±5% RH for Lamotrigine

Time in minutes	Cumulative percentage drug release		
	Initial N = 3 mean ± SD	After 3 months N = 3 mean ± SD	After 6 months N = 3 mean ± SD
2	61.6±0.2	61.2±0.2	61.7±0.4
4	70.6±0.43	70.8±0.14	70±0.12
6	81.1±0.09	81.6±0.34	81.9±0.13
8	88.48±0.00	88.2±0.10	88±0.62
10	93.8±0.64	93.7±0.38	93.2±0.53

Values are expressed as mean±SEM. SEM: Standard error of mean; SD: Solid dispersion; RH: Relative humidity

Table 8: Pharmacokinetic parameters of fast-dissolving tablets of Lamotrigine

Pharmacokinetic parameters	Pure drug	Prepared formulation	Marketed formulation
Peak plasma concentration C_{max} (µg/ml)	80.44	200.87	94.66
Time to reach peak plasma concentration T_{max} (h)	1.5 h	0.5 h	1 h
Biological half-life $t_{1/2}$ (h)	24.54	24.55	24.58
Elimination rate constant K_e (h ⁻¹)	0.0282	0.028	0.0281
Area under the curve (total) (µg/ml h*)	251.45	740	321.57

show high significance. The present study was also comparable to that of enhancement of the dissolution rate prepared by the melt method using poloxamer 407 (L 127). In that study, the results of solid state characterization performed by Fourier transform infrared spectroscopy, differential scanning calorimetry and powder X-ray diffractometry techniques revealed a decrease in the crystallinity of LM that might be accounting for improvement in the dissolution properties as seen from dissolution studies.^[22]

Furthermore, the fast-dissolving tablets of LM were successfully prepared by using containing ac-di-sol and crospovidone as super disintegrants. The *in vivo* studies clearly indicated that SD approach can be adopted for formulation of LM tablets in order to achieve a faster onset of action.

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