Original Research Article

Formulation Development and evaluation of fast disintegrating tablets of Lamotrigine using *liqui-solid* technique

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Abstract

Introduction: Epilepsy is a serious neurological disorder. Lamotrigine is an alternative to lithium for the treatment of epilepsy, and its oral bioavailability is 98%; however, its poor aqueous solubility hinders its oral absorption. Among the techniques available to enhance the solubility, dissolution rate and bio availability of poorly soluble drugs, *liqui-solid* technique is a novel and promising approach. The objectives of the investigation are to formulate, optimize lamotrigine *liqui-solid* compacts using 2^3 factorial experiments, validate experimental designs statistically and to compare with the marketed tablets using similarity and difference factors. **Materials and Methods:** Based on solubility studies tween 20 as nonvolatile liquid, avicel pH 101 as a carrier and aerosil 200 as a coating material were used. Liquid load factor other flow and compression characteristics were determined for different ratios of carrier and coat materials. Suitable quantities of carrier and coat materials were taken, according to the experimental designs other excipients were added, *liqui-solid* tablets were prepared by direct compression and evaluated. Drug excipient compatibility was determined using Fourier transform infrared spectroscopy (FTIR) analysis. The hardness, disintegration time and T75% were considered for validation of experimental designs. **Results:** The physicochemical properties of tablets such as hardness (1.5 ± 0.8–4.95 ± 0.96 kg), *in vitro* disintegration time (40 ± 20–320 ± 25 s) and Friability (0.39 ± 0.5–1.45 ± 0.2% also <1%) possess all the Indian pharmacopoeal requirements. The T75% was calculated and found to be 6.62–22.8 min. The rate of drug release followed first order kinetics. f_1 and f_2 values indicated the similarity in dissolution profiles between marketed and the optimized formulation and 63.64% similar with that of the marketed fast disintegrating tablets. FTIR studies revealed the absence of drug excipient incompatibility.

Key words: Bipolar disorder, difference factor, direct compression, epilepsy, the polynomial equation, the similarity factor

INTRODUCTION

Bipolar disorders such as epilepsy are serious neurological disorders affecting a population of 50 million people worldwide. These disorders are recurrent and cannot be predicted. The incidences of these disorders in patients with and without epilepsy are 94.1 and 22.6/1000 persons in every year.[1] Today the average age of bipolar disorder is 19 years and the situation is more severe because 40% of persons with bipolar disorders abuse alcohol or drugs, 15-25% die by suicide, accident or are killed in altercations triggered in a maniac phase and >90% of marriages involving a partner with bipolar disorder end in divorce.[2] Lamotrigine is the first drug approved by Food and Drug Administration (FDA) as an alternative to the lithium for long term maintenance and treatment of bipolar disorders. Studies reported that the lamotrigine significantly delays the incidence of repeat episodes. Lamotrigine is a mood elevating mood stabilizer and causes few side effects and is well-tolerated by the patient. Chemically Lamotrigine is 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine. It works by inhibiting voltage dependent sodium channels, resulting in decreased release of the excitatory neurotransmitters glutamate and aspartate-2. It has an elimination half-life of longer than 24 h., so once or twice daily dosing is possible in all patients. Lamotrigine is rapidly and completely absorbed after oral administration with negligible first-pass metabolism (absolute bioavailability is 98%). However, as it belongs to BCS class II, the absorption and bioavailability is the dissolution rate limited. To enhance the solubility and dissolution rate of lamotrigine several dosage forms such as

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Microcrystals,[3] micro emulsions,[4] Lamotrigine pellets using solid dispersion technique[5] and crystal forms of lamotrigine have been developed. All these dosage forms present some unique problems which include difficulty in scale up process (micro crystals), poor physical stability (micro emulsions), more number of processing steps and poor yield value (pelletization using solid dispersion technique) make them useless. Among various techniques available *liqui-solid* technique is most promising method to promote dissolution rate of poorly soluble drugs.[6] The term *liqui-solid* system is a powdered form of liquid drug formulated by converting liquid lipophilic drug or drug suspension or solution of water insoluble solid drug in suitable nonvolatile solvent systems into dry looking, nonadherent, free flowing and readily compressible powdered mixtures by blending with selected carrier and coating materials.[7] The primary objective of the present investigation is to formulate lamotrigine a poorly soluble drug into *liqui-solid* compacts using tween 20 as nonvolatile liquid and to optimize the formulation variables using 2^3 factorial designs. The second objective is to evaluate the prepared tablets, to validate the experimental designs and to calculate similarity factor and difference factor between the formulated *liqui-solid* compacts and the marketed tablets.

MATERIALS AND METHODS

Materials

Lamotrigine was obtained as a gift sample from Jubilant life sciences limited, Noida, India. Sodium starch glycolate (SSG), Crosspovidone, Microcrystalline Cellulose (Avicel PH 102), Aerosil, Acacia, Magnesium Stearate, Talc, tween 20 and tween 80 were purchased from Himedia laboratories private limited, India.

Methods

Preparation of the calibration curve

Primary stock solution (1 mg/ml of lamotrigine in methanol) was prepared. From the primary stock solution secondary stock was prepared using 0.1 N HCl, pH 1.2 to produce 100 µg/ml. From the secondary stock solution calibration curve standards (2, 4, 6, 8 and 10 mcg/ml) were prepared using 0.1 N HCl, pH 1.2. From the calibration curve standards, 10 µg/ml was scanned over a range 200-400 nm using ultraviolet (UV) visible spectrophotometer to determine its λ_{max}. The peak was observed at the 275 nm for lamotrigine. The absorbance was measured for all the calibration curve standards at 275 nm and a linear graph was plotted between concentration versus absorbance.

Solubility studies and selection of nonvolatile solvent[8]

High boiling point, inert, low viscous and water miscible organic solvents such as propylene glycol, tween 20, tween 80, polyethylene glycol 400 were selected and 1% solutions in water was prepared. From each of these solutions 10 ml was taken, excess quantity of drug was added and saturated solutions were prepared by shaking on a mechanical shaker. The saturated solutions were kept aside overnight, filtered and appropriate dilutions were made, and the absorbance was measured at 275 nm using Systronics double beam UV visible spectrophotometer.

Selection of carrier and coat material ratio and calculation of liquid load factor

From the solubility studies tween, 20 was selected as nonvolatile liquid for the preparation of *liqui-solid* compacts. For the present study microcrystalline cellulose (Avicel pH 101) and aerosol PH 200 were used as carrier and coating materials respectively. Mixtures of carrier and coating materials in different ratios viz., S1 (1:4), S2 (2:3), S3 (3:2) and S4 (4:1) were prepared and load factor was determined by adding a quantity of tween 20 in small increments to obtain a free flowing powder using a mortar and pestle. The consistency, flow ability and compressibility characteristics were determined.[9,10]

Loading factor is calculated by $Lf = W/Q$

Where,
W = Amount of liquid medication.
Q = Amount of the carrier material.

Determination of flow ability and compressibility characteristics

Bulk density and tapped density

Bulk density (BD) and tapped density (TD) were determined for all the ratios of the above mixtures separately by passing through a sieve with an aperture equal to 1 mm to break the lumps, if any. Then, accurately weighed quantity of the above mixture was placed in 100 ml graduated measuring cylinder. Initial bulk volume (Vo) was observed. The cylinder was tapped initially 500 times and then 750 times from a distance of 14 ± 2 mm. The tapped volume (Vf) was measured to the nearest graduated unit. The BD and TD were calculated in grams per ml using following formulae,

BD = weight of the powder/bulk volume of the packing
TD = weight of the powder/final tapped volume of the packing.

Compressibility index (Carr's indices)

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. Compressibility is calculated by using the following formula

$$CI = 100\ (V_o - V_f)/V_o$$

Where,
Vo = Initial volume,
Vf = Final volume

In theory, the less compressible a material, the more flow able it is. A material is having values of <5-12% compressibility index is defined as a free flowing material.[11]

Determination of the angle of repose

Angle of repose is determined by placing a hopper to the stand at a certain height of 2 cm distance from the bottom where

graph paper was placed. The sample is placed in the hopper and allowed to flow through the hopper and fall on the graph sheet. The height of the pile is measured by using a scale gives the value 'h' and the diameter of the pile is measured and half of which gives the value of 'r' and angle of repose is calculated using the following formula.

$$\emptyset = \tan - 1 \frac{H}{R}$$

Where,
H = Height of the powder cone,
R = Radius of the powder cone.

Preparation of *liqui-solid* compacts of lamotrigine using 2^3 factorial experimental designs

Based on flow ability properties, and load factor S4 ratio was selected and 2^3 factorial experimental designs was adapted for optimization of formulation variables and shown in Table 1. The three independent factors considered here include Crosspovidone (factor A), sodium starch glycollate (factor B) and acacia (factor C). All factors were used at two levels, and the assigned values were given in Table 2. The dependent responses measured were crushing strength, disintegration time and dissolution time T75%. A weighed quantity of Lamotrigine was initially dispersed in the nonvolatile solvent tween 20 and the mixture of carrier (avicel) and coating (aerosil) material (from the selected ratio 2:3) were added under continuous mixing in a mortar.[12,13]

A quantity of this binary mixture equivalent to 25 mg of lamotrigine per tablet was taken into the mortar. To this disintegrant and other additives were added according to their application and mixed for a period of 5-10 min. Then, the final mixture was compressed using ELITE multi station punching machine using 7.5 mm flat punches and the compositions prepared were depicted in Table 3.

Table 1: 2^3 factorial experimental designs

Code	Factor A (cross povidone)	Factor B (SSG)	Factor C (acacia)
(1)	−	−	−
A	+	−	−
B	−	+	−
Ab	+	+	−
C	−	−	+
Ac	+	−	+
Bc	−	+	+
Abc	+	+	+

SSG: Sodium starch glycolate

Table 2: All factors used at two levels and the assigned values

Factor	Level	Symbol	Assigned value
A	Low	−	0 mg
A	High	+	10 mg
B	Low	−	0 mg
B	High	+	10
C	Low	−	15 mg
C	High	+	20 mg

Table 3: Composition of lamotrigine *liqui-solid* tablets

Code/ingredient	X1	X2	X3	X4	X5	X6	X7	X8
Lamotrigine + carrier and coating materials (mg)	100	100	100	100	100	100	100	100
Avicel (mg)	50	50	50	50	50	50	50	50
Sodium starch glycolate (mg)	0	0	10	10	0	0	10	10
Crosspovidone (mg)	0	10	0	10	0	10	0	10
Acacia (mg)	15	15	15	15	20	20	20	20
Magnesium stearate (mg)	5	5	5	5	5	5	5	5
Talc (mg)	5	5	5	5	5	5	5	5
Total tablet weight (mg)	175	185	185	195	180	190	190	200

Evaluation of liqui-solid tablets

Uniformity of weight

Randomly selected 10 tablets were weighed individually and together in a single pan balance. The average weight was noted, and standard deviation was calculated. USP limit for weight variation in case of tablets weighting up to 130 mg is ±10%, 130-324 mg is ±7.5% and >324 mg is ±5%.

Tablet hardness

Hardness or tablet crushing strength is the force required to break a tablet in a diametric compression test and was measured using Monsanto tablet hardness tester. A tablet hardness of about 2-4 kg/cm^2 is considered adequate for mechanical stability.

Tablet friability

Friability of tablets was measured by using Roche Friabilator. Friability was evaluated from the percentage weight loss of 20 tablets tumbled in a friabilator at 25 rpm for 4 min. The tablets were de dusted, and the loss in weight caused by fracture or abrasion was recorded as the percentage weight loss. Friability below 1% was considered as acceptable.

$$\% \text{ friability} = ([\text{Initial weight} - \text{Final weight}]/\text{initialweight}) \times 100$$

Disintegration time

The test was carried out on 6 tablets using tablet disintegration tester ED-20 (Electro lab, Mumbai, India) and 0.1N HCL at 37°C ± 2°C was used as a disintegration media and the time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured.

Determination of drug content

Randomly selected ten tablets were powdered in a mortar. From this powder, a quantity equivalent to 10 mg of lamotrigine was transferred in to a 10 ml volumetric flask containing 5 ml of methanol and shaken for 15 min. Then the volumetric flask was made up to the volume with methanol. Then the solution was filtered, and appropriate dilutions were made to produce 10 mcg/ml solution of lamotrigine and absorbance was measured

at 275 nm using double beam spectrophotometer. Drug content was calculated from standard calibration curve.

In vitro dissolution profile of prepared lamotrigine liqui-solid tablets[11]

The *in vitro* release rate of lamotrigine from *liqui-solid* tablets was determined using Dissolution Tester (USP type-II)-eight baskets paddle model. The dissolution test was performed using 900 ml of 0.1 N HCl (pH = 1.2), at 37°C ± 0.5°C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at 5, 10, 15, 20, 30, and 45 min. The samples were replaced with fresh dissolution medium of the same quantity. The samples were filtered through whattman filter paper. Absorbance of these solutions was measured at 275 nm using a double beam UV/visible spectrophotometer. Cumulative percentage of drug release was calculated from the standard curve. T75% values are calculated using first order rate equation.

Methods to compare dissolution profiles

Model dependent methods

Lamotrigine release kinetics was analyzed by various mathematical models, which were applied by considering the amount of drug released in 0-40 min. Based on these estimations; mathematical models were described for dissolution profiles. The model fitting was represented in the form of plots such as cumulative percent drug release versus time (zero order kinetic model), log cumulative percent drug remaining versus time (first order kinetic model), cube root of percent drug remaining versus time (Hixon-Crowell cube root law).

Model independent method[11]

A model independent method for the comparison of the *in vitro* release profiles of optimized *liqui-solid* tablet formulation and marketed tablets were carried out by determining the similarity factors (f_2) and difference factor (f_1), using the following equations.

Similarity factors (f_2) equation:

$$f_2 = 50 \times \log \{[1 + (1/n) \Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \times 100\}$$

Difference factor (f_1) equation:

$$f_1 = \frac{\sum_{t=1}^{n} R_t - T_t}{\sum_{t=1}^{n} R_t} \times 100$$

Where,

n = Number of time points at which percent dissolved was determined,

R_t = The percent dissolved of reference (marketed) formulation at a given time point

T_t = The percent dissolved of the test formulation to be compared at the same time point.

Validation of experimental designs

In order to validate the experimental designs, the following polynomial equation was used and the three responses measured were crushing strength, disintegration time and drug dissolution T75%.

$$Y = B0 + B1A + B2B + B3C + B12 (AB) + B13 (AC) + B23 (BC) + B123 (ABC)$$

Where Y represents the experimental response, B0 the intercept and B1-B123 are the coefficients for the factors A (crosspovidone), B (Sodium starch glycollate) and C (Acacia). All tests were performed at 95% level confidence level ($P > 0.05$). In the final model equation, only the significant factors were included. The polynomial equation was applied on the response parameters, disintegration time, crushing strength independently and dissolution time T75%. The theoretical responses for disintegration time, crushing strength and dissolution time T75% were calculated using Microsoft Office Excel 2007.[15]

Drug excipient compatibility studies

Infrared spectra analysis was carried out for the final optimized formulation of *liqui-solid* tablets by KBr pellet method using Fourier transform infrared spectroscopy (FTIR). FTIR spectrum of the *liqui-solid* tablets and pure drug was compared.

RESULTS AND DISCUSSION

Standard calibration curve of lamotrigine

The absorbance of the solution was measured at 275 nm, using UV spectrometer with 0.1N HCl. A graph of absorbance versus concentration was plotted which indicated in compliance to Beer's law in the concentration range and this analytical method was used for the analysis of all samples.

Solubility studies and selection of nonvolatile solvent

In the preparation of liquid solid compacts nonvolatile liquid plays the major role. For the present study nonvolatile solvents such as tween 20, propylene glycol and polyethylene glycol 400 were chosen and solubility of lamotrigine was checked in order to select the suitable liquid.[16] From the solubility studies it is found that lamotrigine exhibited highest solubility in tween 20 (49.4 ± 0.65) and the results were given in Figure 1.

Selection of carrier and coat material ratio and calculation of loading factor

Liquid load factor is defined as the ratio of the weight of liquid medication over the weight of carrier material in the system. An acceptably flowing and compressible system can be obtained only if a maximum liquid on the carrier material is not exceeded and therefore liquid load factor is calculated in order to select the suitable quantity of liquid and carrier, coat materials.

Avicel 102 and aerosil PH 200 were used as carrier and coat materials respectively, various ratios were prepared and liquid load factor was calculated and was depicted in Table 4. Avicel PH 102 is a porous material, has good compressibility and absorption

properties, which contributes in liquid absorption. Aerosil 200 is very fine and highly adsorptive in nature and therefore contributes in covering the wet carrier particles and imparts flow ability characteristics to the *liqui-solid* compacts. The flowability of powder is a critical factor in the production of pharmaceutical dosage forms to reduce the dose variations.

Precompression characteristics of lamotrigine liqui-solid compacts

Hence flow properties viz., angle of repose, BD and compressibility index were determined and given in Table 5. BD, was found in the range of 0.280-0.412 g/cm^3 and the TD between 0.295 and 0.457 g/cm^3 and compressibility index was in the range of 3.21-10.60%. This indicates a fairly good flowability of the powder blend. The good flow ability of the powder blend was also indicated by the angle of repose, which is in the range of 24.2-29.68° which is below 40° indicating good flowability.

Preparation of liqui-solid tablets

Accurately weighed quantities of the drug, and nonvolatile liquids were taken in a glass beaker and stirred well with a glass rod in order to dissolve the drug in liquid. This liquid medication was added slowly to the mortar containing carrier coat material blend and triturated to distribute the liquid medication uniformly throughout the powder mixture. This entire powder blend was left aside for 5 min to absorb the liquid by carrier and coat material mixture. Then SSG and other excipients were added and compressed by direct compression technique. Direct compression technique for tablets manufacturing is more commercially acceptable method due to its less number of processing steps. Therefore in the present study, direct compression method is employed.

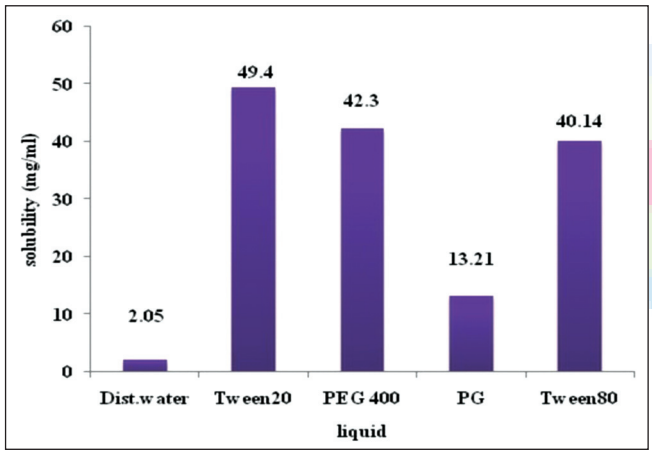

Figure 1: Solubility profiles of lamotrigine in different solvents

Table 4: Key formulation characteristics of lamotrigine *liqui-solid* compacts

Code	Concentration of drug % (W/W) in the liquid vehicle	Avicel-PH 102 (Q)	Aerosil – PH 200 (q)	R = Q/q	L_f
S1	50	100	400	0.25	0.5
S2	50	200	300	0.666	0.25
S3	50	300	200	1.5	0.166
S4	50	400	100	4	0.125

R: Ratio of carrier to the coating material

Evaluation of liqui-solid tablets

The prepared tablets were evaluated for all compendial tests. Since the powder material was free flowing, tablets were obtained of uniform weight due to uniform die fill, with acceptable weight variations as per USP. The hardness of tablet was in between 1.5 ± 0.8 and 4.95 ± 0.96 kg indicating good mechanical strength of the tablets. The *in vitro* disintegration time was found to be between 40 ± 20 s to 320 ± 25 s and friability is 0.39% ± 0.5% to 1.45% ± 0.2% also lass then 1%, which fulfilling the official requirements for tablet as per USP. Weight variation and drug content uniformity were determined for all the *liqui-solid* tablets and marketed tablets. The results confirmed that all the tablets complied with the Indian pharmacopoeial standards in which the individual content was between 85% and 115%. The data was showed in Table 6.

In vitro drug release studies

In vitro drug release profiles of liqui - solid tablets and marketed tablets were illustrated in Figures 2-4. It was observed that within 5 min 19.6% ± 0.45-68.7% ± 0.84% of drug was released, and the drug release was 58.26 ± 1.42-98.23 ± 0.36 and 100.4 ± 0.12 in 0.1N HCl at 25 min in formulations X1 to X8 and marketed formulation respectively. This may be due to the drug that is present on the surface of the tablets dissolve and diffuse in to the dissolution medium. The superdisintegrants also contributed to this burst release affect. The rate of drug release followed first order release rates and is indicated by the first order plots. *Liqui-solid* tablets are containing dissolved drug (in the form of molecular dispersion), the drug surface available for dissolution is highly increased. Hence, molecularly dispersed drug in *liqui-solid* tablets may be responsible for greater dissolution rates and revealed by Hixon-Crowel cube root plots. The dissolution rate was found to increase linearly with increase concentration of superdisintegrants. Formulations which contained increase concentration of SSG have recorded

Table 5: Precompression characteristics of lamotrigine *liqui-solid* compacts

Code/parameter	Angle of repose (°)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index (%)
S1	24.2	0.350	0.342	3.21
S2	29.68	0.331	0.353	6.23
S3	26.45	0.280	0.295	5.08
S4	28.19	0.412	0.457	10.6

Table 6: Postcompression characteristics of *liqui-solid* tablets

Code/parameter	Average weight of the tablet (mg) ± SD	Hardness (kg/cm²)	Friability (%)	Disintegration (s)	Percent drug content uniformity	T75% (min)
X1	179.59±1.2	2.4±0.6	1.45±0.2	300±60	96.8±0.79	25.75
X2	180.6±1.32	2.5±0.2	1.21±0.1	60±30	95.8±0.73	20.6
X3	180.7±1.6	3.1±1	0.44±0.3	40±34	98.34±1.86	12.875
X4	181.06±0.92	1.5±0.8	1.29±0.1	40±20	94.8±0.73	21.45
X5	180.49±1.45	4.95±.96	1.1±0.1	320±25	93.8±0.83	39.61
X6	180±1.4	3±0.4	0.39±0.5	50±23	97.2±0.28	19.8
X7	180.4±2.1	3.5±0.5	0.55±0.2	100±28	99.2±1.76	8.72
X8	180.5±1.06	4.5±0.9	1.25±0.1	90±29	97.8±1.74	19.806
Marketed	100±1.2	4.2±0.8	1.25±0.6	30±25	98.12±0.1	8.17

SD: Standard deviation

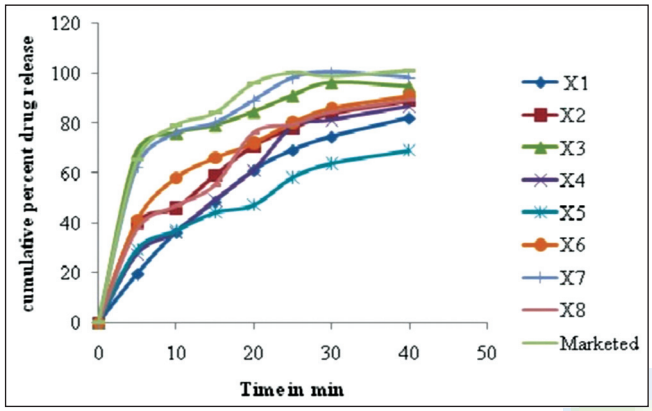

Figure 2: cumulative percent drug released in fast disintegrating *liqui-solid* and marketed tablets of lamotrigine in 0.1N HCl

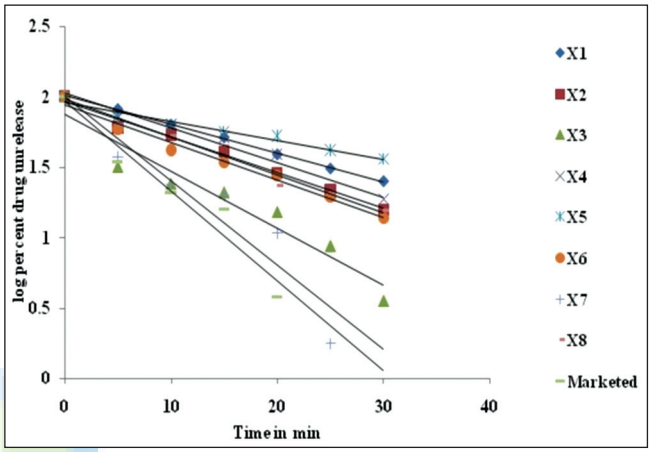

Figure 3: Log percent drug unreleased versus time of *liqui-solid* and marketed tablets of lamotrigine

drug release 93.2%, 98.4% and 100.5% respectively at the end of 40 min. Formulations which contained increased concentration of crosspovidone have recorded drug release 89.18%, 91.21% respectively at the end of 40 min. According to the US FDA regulations is the test product and the reference product show >85% dissolution within 15 min the profiles are considered to be similar. If no similarity factor (f_2) provides a simple way to compare dissolution data.

US FDA guidance proposes that f_2 values of 50-100% indicate equivalence in dissolution profiles. f_1 and f_2 values were showed in Table 7. Batches showing f_2 values >50%; which indicates similarity in dissolution profile. The f_1 value found to be 10% and the difference is only 10% between *liqui-solid* tablets and marketed tablets. To compare the dissolution profiles of two products the conditions of dissolution testing for example volume of the dissolution media, temperature must be similar. Samples should be drawn at same time points and excluding zero, at least the samples should be drawn for 3 time points. The strength or weight of the dosageform/tablet may not be the same.

Validation of experimental designs

The factor effects were described by the polynomial equations. In the equation 1 the negative coefficient for factors A and B indicates that with increasing disintegrant concentration the crushing strength, disintegration time and T75% were decreased and the positive coefficient for factor C all the responses were increased.

$$Y1 = -2.125 - 0.0612A - 0.00625B + 0.3225C + 3.519AB - 2.16AC - 2.43BC \quad (1)$$

$$Y2 = 142.5 - 13A - 11.5B + 6C + 247.5AB + 77.5BC + 85AC \quad (2)$$

$$Y3 = 9.43 - 0.115A + 0.4025B + 0.2C + 0.4025AB - 0.0075AC + 0.1625BC \quad (3)$$

A: Crosspovidone, B: Sodium starch glycollate, C: Acacia, Y1: Hardness, Y2: Disintegration time, Y3: Dissolution T75%

Drug excipient compatibility studies

Drug excipient compatibility studies were carried out by FTIR, and the results were given in the Figures 5 and 6. FTIR studies revealed that there are no drug excipient interactions.

CONCLUSIONS

The fast disintegrating tablets of lamotrigine were prepared by *liqui-solid* technique using different super disintegrating such as crosspovidone, SSG. The relative efficiency of these super

Table 7: Similarity factor (f_2) and difference factor (f_1) values of *liqui-solid* formulation (X7) compared with marketed tablet

Comparison	f_2 value	f_1 value (%)	Dissolution profile
Optimized formulation (X7) and marketed tablet	63.64	10	Similar

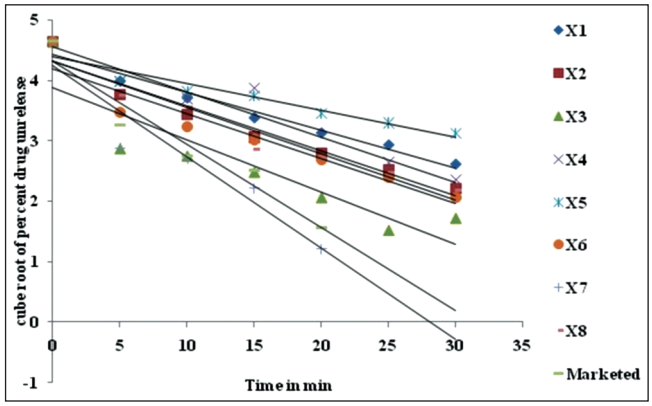

Figure 4: Hixon-Crowel dissolution plots of *liqui-solid* tablets of lamotrigine

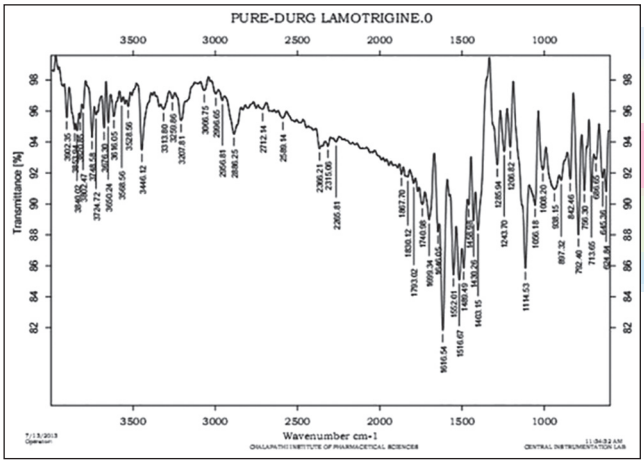

Figure 5: Infrared spectrum of lamotrigine

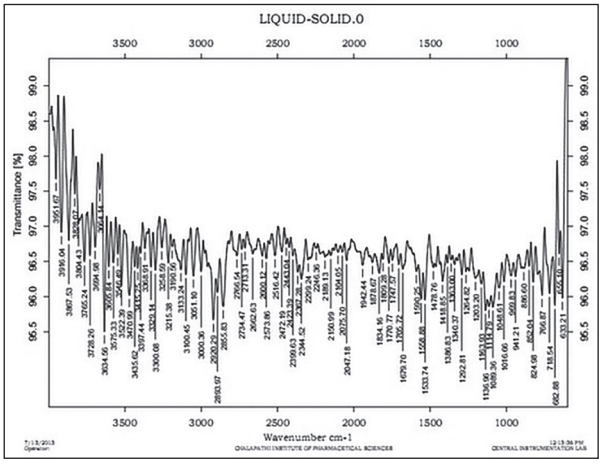

Figure 6: Infrared spectrum of *liqui-solid* formulation results

disintegrating to improve the disintegrating and dissolution rates of tablets was in order to SSG> crosspovidone. The rate of drug release followed first order kinetics, and the data was fit into the Hixon-Crowel cube root law indicating the mechanism of drug release. Similarity factor and difference factor were calculated between marketed formulation and optimized liqui-solid formulation and found to be f_2 = 63.64 and f_1 = 10%. Therefore, the marketed formulation and *liqui-solid* formulation were considered to be similar in *in vitro* dissolution profiles. Drug excipient compatibility studies were carried out and found no drug excipient interactions.

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