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RESEARCH ARTICLE

Formulation Design and Development of Fast Disintegrating Tablets of "Lamotrigine" Using Liqui-Solid Technique

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ABSTRACT

Epilepsy is a disorder characterized by seizures which take various forms and result from episodic neuronal di Epilepsy is a neurological condition that is characterized by recurrent seizures. A seizure occurs when abnormal electrical activity affects a part or all parts of the brain. scharges, the form of seizure depending upon the part of brain affected. Fast dissolving dosage forms can be disintegrated, dissolved, or suspended by saliva in the mouth. Fast dissolving tablets are useful in patients, like pediatric, geriatric, bedridden, or mentally disabled. Construction of calibration curve Solubility studies and selection of non volatile solvent Selection of carrier and coat material ratio and calculation of loading factor Formulation of lamotrigine fast disintegrating tablets by liqui solid technique. Evaluation of powder blend for pre compression parameters such as Angle of repose, Bulk density, Tapped density and compressibility index Evaluation of Post compression Characteristics of Lamotrigine fast disintegrating liqui-solid tablets such as weight variation, Hardness, Friability, Disintegration and Dissolution tests. Application of mathematical models. I.e. is zero order, first order, hixon- crowel models to the *in-vitro* dissolution data Drug excipient compatibility studies using FT-IR Compilation and documentation of the data.

KEYWORDS

Epilepsy, Calibration, FT-IR, Lamotrigine

INTRODUCTION

Epilepsy[1]

Epilepsy is a disorder characterized by seizures which take various forms and result from episodic neuronal discharges, the form of seizure depending upon the part of brain affected.

Definition of Epilepsy[1]

Epilepsy may be defined as a paroxysmal, abnormal cerebral electrical discharge associated with a clinical change taking a variety of forms, but usually including some impairment of consciousness.

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The Nature of Epilepsy[2,3]

Epilepsy is a neurological condition that is characterized by recurrent seizures. A seizure occurs when abnormal electrical activity affects a part or all parts of the brain. A seizure can last for seconds or minutes depending on the type of seizure. In addition, the symptoms are different depending on the type of seizure. Epilepsy can be caused by numerous conditions affecting the brain, and in many cases there is no specific cause identified. The centers for disease control and Prevention states that, "Epilepsy affects

about 2.0 million Americans every year. Approximately ten percent of the population will have some kind of seizure during their lifetime; however, that does not necessarily make them epileptic. When a person has two or more seizures, they are considered to have epilepsy.

Epilepsy occurs when brain tissue is permanently changed and the neurons become overly excitable. When neurons are overly sensitive, they send irregular electrical signals, which cause seizures. There are many common causes of epilepsy, including stoke, traumatic brain injury, infections, congenital defects, brain tumors, and abnormal blood vessels in the brain. When the seizures have an identifiable cause, such as any of the mentioned, then they are labeled symptomatic seizures.

When the seizures are diagnosed with no cause then they are labeled cryptogenic seizures. Epilepsy may have genetic components, and when the cause is thought to have come from heredity then an idiopathic diagnosis is made. In addition, the causes of seizures can be further categorized into acute or remote. Acute is when there is an active cause, such as an infection that provokes seizures during the illness.

Fast Disintegrating Tablets[4]

Fast dissolving dosage forms can be disintegrated, dissolved, or suspended by saliva in the mouth. Fast dissolving tablets are useful in patients, like pediatric, geriatric, bedridden, or mentally disabled. To improve the ease of administration, the fast dissolving tablet is the most widely preferred commercial products.

The oral cavity is an Attractive site for the administration of drugs because of ease of administration. Various dosage forms are administered by oral route like Tablets, Capsules, Liquid preparations, etc.

During the last decade, mouth dissolving tablet (MDT) and fast dissolving tablet (FDT) technologies that make tablets disintegrate in the mouth without chewing and intake of additional water have been used to produce quick onset of action.

MATERIALS AND METHOD

Preparation of Calibration Curve

Primary stock solution (1mg/ml of lamotrigine in methanol) was prepared. From the primary stock solution secondary stock was prepared using 0.1N HCl (p^H1.2) to produce 100 µg/ml. From the secondary stock solution calibration curve standards (2, 4, 6, 8 and 10 mcg/ml) were prepared using 0.1N HCl (p^H1.2) From the calibration curve standards 10 µg/ml was scanned over a range 200 – 400 nm using UV Visible spectrophotometer to determine its λ_{max}. The peak was observed at the 275nm for lamotrigine. The absorbance was measured for all the calibration curve standards at 275 nm and a linear graph was plotted between concentration v_s absorbance.

Solubility Studies and Selection of Non Volatile Solvent[5]

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 percent 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 Systronic double beam UV visible spectrophotometer.

Selection of Carrier and Coat Material Ratio and Calculation of Liquid Load Factor[6]

From the solubility studies tween 20 was selected as non-volatile liquid for the preparation of liqui solid compacts. For the present study microcrystalline cellulose (Avicel PH101) 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.

Loading factor is calculated by

$$L_f = W/Q$$

Where,

W= Amount of liquid medication.

Q = Amount of carrier material

Determination of Flowability and Compressibility Characteristics

Bulk Density[7, 8]

Bulk density (BD) and tapped density (TD) were determined for all the ratios of the above mixtures separately by passing through a #18 sieve to break the clumps, if any. Then accurately weighed quantity of the above mixture was placed in a 100 ml graduated measuring cylinder. Initial volume was observed. The cylinder was tapped initially 500 times from a distance of 14 + 2 mm. The tapped volume (Va) was measured to the nearest graduated unit. The tapping was repeated additional 750 times. Again the tapped volume was measured to the nearest graduated unit. The BD and TD were calculated in g per ml using following formulae,

BD = weight of the powder/volume of the packing

TD = weight of the powder/tapped volume of the packing

Compressibility Index (Carr's Indices) [9, 10]

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

$$C_I = 100 (V_O - V_f) / V_o$$

Where,

Vo = Initial volume

Vf = Final volume

In theory, the less compressible a material the more flowable it is. A material having values of less than 5 to 12 % compressibility index is defined as the free flowing material.

Determination of Angle of Repose[11, 12]

Angle of repose is determined by placing a hopper to the stand at a certain height of 2cm distance from the bottom where graph paper was placed. The sample is placed in the hopper and allowed to flow through the hopper and falls on the graph sheet. The height of the pile is measured by using 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 Liquid- Solid Compacts of Lamotrigine Using 2^3 Factorial Experimental Designs[13,14]

Based on flow ability properties and load factor S4 ratio was selected and a 2^3 factorial experimental designs was adapted for optimization of formulation variables. The three independent factors considered here include Crosspovidone (factor A), sodium starch glycollate (factor B) and acacia (factor C). 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. A quantity of this binary mixture equivalent to 25mg of lamotrigine per tablet was taken in to a mortar. To this disintegrant and other additives were added according to their application and mixed for a period of 5 to 10 minutes. Then the final mixture was compressed using ELITE multi station punching machine using 7.5 mm flat punches and the compositions prepared were depicted *100 mg of lamotrigine

+ carrier & coating materials mixture is equivalent to 25 mg of drug.

Validation of Experimental Designs[15]

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%.

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

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 Excel 2007.

Evaluation of Liquid Solid Tablets

Uniformity of Weight

Randomly selected 20 tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation was calculated. IP limit for weight variation in case of tablets weighting up to 80 mg is ± 10%, 80 mg to 250 mg is ± 7.5% and more than 250 mg is ± 5%.

Tablet Hardness[16]

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[16]

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 25rpm 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 acceptable.

% Friability = [(Initial weight – Final weight) / initial weight] × 100

Disintegration Time[16]

The test was carried out on 6 tablets using Tablet disintegration tester ED-20 (Electro lab, Mumbai, India) and 0.1N HCL at 37ºC ± 2ºC 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 a10 ml volumetric flask containing 5ml of methanol and shaken for 15 minute. Then the volumetric flask was made up to the volume with methanol. Then the solution was filtered and appropriate dilutions were made to produce 10mcg/ml solution of lamotrigine and absorbance was measured at 275nm using double beam spectrophotometer. Drug content was calculated from standard calibration curve.

In Vitro Dissolution Profile of Prepared Lamotrigine Liqui-Solid Tablets[17,18]

The in vitro release rate of Lamotrigine from liquid-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 (p^H=1.2), at 37 ±0.5°C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at 5, 10, 15, 20, 25, 30, and 40 min. The samples were replaced with fresh dissolution medium of same quantity. The samples were filtered through whatman 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 standard curve.

Methods to Compare Dissolution Profiles

Model Dependent Methods[19]

Lamotrigine release kinetics was analyzed by various mathematical models, which were applied by considering the amount of drug released in 0 to 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

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($f2$) and difference factor (f_1), using the following equations.

Similarity factors (f_2) equation

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

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.

Drug Excipient Compatibility Studies

Infra - red spectra analysis was carried out for the final optimized formulation of liquid solid tablets by KBR pellet method using Fourier transform infrared spectroscopy. An IR spectrum of the liquid solid tablets and pure drug was compared.

RESULTS

Standard Calibration Curve of Lamotrigine

Table 1: Standard calibration curve values of Lamotrigine

Sr. no	Concentration (µg/ml)	Absorbance(nm)
1)	2 µg/ml	0.19 nm
2)	4 µg/ml	0.362 nm
3)	6 µg/ml	0.52 nm
4)	8 µg/ml	0.69 nm
5)	10 µg/ml	0.852 nm

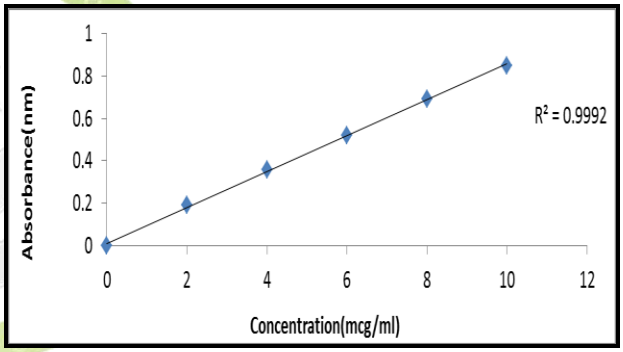

Figure 1: Standard Calibration curve of lamotrigine

Solubility Studies and Selection of Non Volatile Solvent

Table 2: Solubility profiles of lamotrigine in nonvolatile liquids

Sr. no	Liquid	Solubility (mg/ml)
1)	Distilled water	2.05 ± 0.12
2)	**Tween 20**	**49.4 ± 0.65**
3)	Polyethylene glycol 400	42.3 ± 0.52
4)	Propylene glycol	13.21 ± 0.12
5)	Tween 80	40.14 ± 0.52

Selection of Carrier and Coat Material Ratio and Calculation of Loading Factor Compacts

Table 3: Key formulation characteristics of lamotrigine liqui-solid

Code	Concentration of drug %(W/W) in liquid vehicle	Avicel-PH102 (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

Pre-Compression Characteristics of Lamotrigine Liqui-Solid Compacts

Table 4: Pre-Compression characteristics of lamotrigine liqui-solid Compacts

Code /parameter	Angle of repose(º)	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

Evaluation of Liqui Solid Tablets

Table 5: Post compression characteristics of liqui - solid tablets

Code /parameter	Average weight of the tablet (mg)±SD	Hardness (kg/cm2)	Friability (%)	Disinte-gration (seconds)	Drug content uniformity	T75%
X1	179.59±1.2	2.4±0.6	1.45±0.2%	300±60sec	96.8±0.79	16.29
X2	180.6±1.32	2.5±0.2	1.21±0.1%	60±30sec	95.8±0.73	13.51
X3	180.7±1.6	3.1±1	0.44±0.3%	40±34sec	98.34±1.86	11.627
X4	181.06±0.92	1.5±0.8	1.29±0.1%	40±20sec	94.8±0.73	13.51
X5	180.49±1.45	4.95±.96	1.1±0.1%	320±25sec	93.8±0.83	22.801
X6	180±1.4	3±0.4	0.39±0.5%	50±23sec	97.2±0.28	13.51
X7	180.4±2.1	3.5±0.5	0.55±0.2%	100±28sec	99.2±1.76	6.62
X8	180.5±1.06	4.5±0.9	1.25±0.1%	90±29 sec	97.8±1.74	13.16
Marketed	100±1.2	4.2±0.8	1.25±0.6%	30±25sec	98.12±0.1	

In Vitro Drug Release Studies

Table 6: Cumulative Percent drug released of lamotrigine liqui- solid tablets

Time (min)	X1	X2	X3	X4	X5	X6	X7	X8	Marketed tablets
5	19.6±0.45	39.69±0.85	68.70±1.5	27.66±0.85	29.42±1.85	41.1±1.25	62.71±0.74	37.61±1.85	65.38±0.86
10	36.3±0.92	46.1±0.82	76.17±0.25	36.4±0.25	36.9±1.81	58.2±0.74	76.0±0.61	46.94±1.82	79.2±0.71
15	48.53±0.72	59.23±0.65	79.18±0.69	49.23±1.65	44.23±0.65	66.2±0.61	80.12±0.86	55.29±0.65	84.15±0.91
20	61.18±0.94	71.18±0.72	84.71±0.5	61.28±1.72	47.18±2.01	72.19±0.81	89.18±1.02	76.38±0.72	96.18±0.34
25	69.27±0.56	78.21±0.56	91.25±0.41	78.54±1.56	58.26±1.42	80.32±0.23	98.23±0.36	79.61±0.56	100.4±0.12
30	74.6±0.87	84.0±0.67	96.47±0.31	81.4±0.37	64.0±1.67	86.21±0.95	100.5±0.45	84.67±0.67	98.9 ±0.2
40	82.18±0.56	89.18±0.54	94.91±0.98	86.84±1.54	69.18±0.69	91.21±1.23	-	89.58±1.54	101.2±0.98

Table 7: *In vitro* drug release profiles of Lamotrigine liquid solid tablets representing log percent drug Unreleased

Time in min	X1	X2	X3	X4	X5	X6	X7	X8	Marketed tablets
5	1.91	1.78	1.50	1.86	1.85	1.77	1.57	1.80	1.54
10	1.80	1.73	1.38	1.80	1.80	1.62	1.38	1.72	1.32
15	1.71	1.61	1.32	1.71	1.75	1.53	1.30	1.65	1.20
20	1.59	1.46	1.18	1.59	1.72	1.44	1.03	1.37	0.58
25	1.49	1.34	0.94	1.33	1.62	1.29	0.25	1.31	-
30	1.40	1.20	0.55	1.27	1.56	1.14	-	1.19	0.04
40	1.25	1.03	0.71	1.12	1.49	0.94	0.18	1.02	-

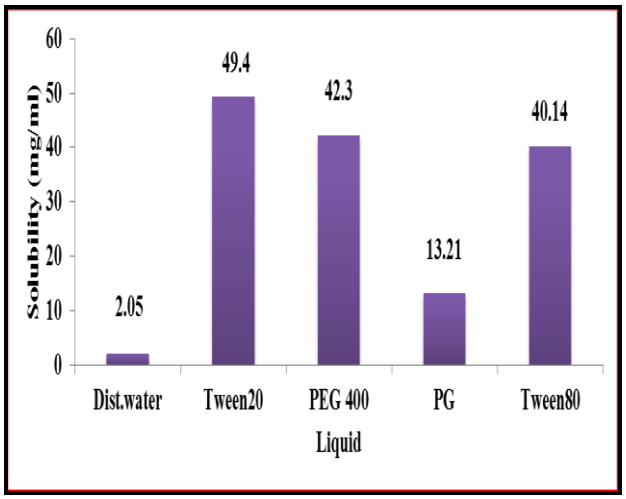

Figure 2: Solubility studies of Lamotrigine in different solvents

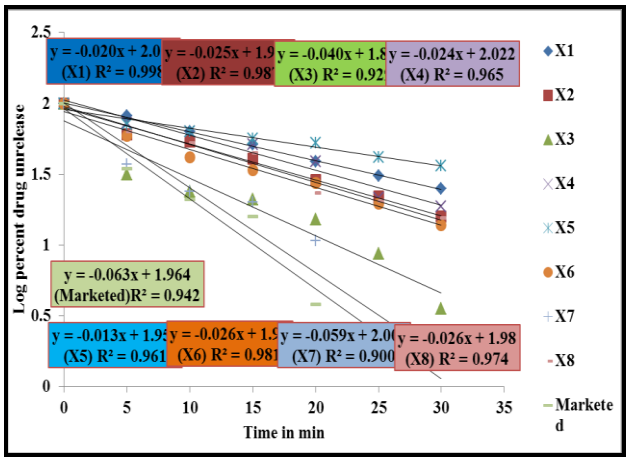

Figure 4: Log percent drug unreleased vs time of liqui solid tablets of lamotrigin

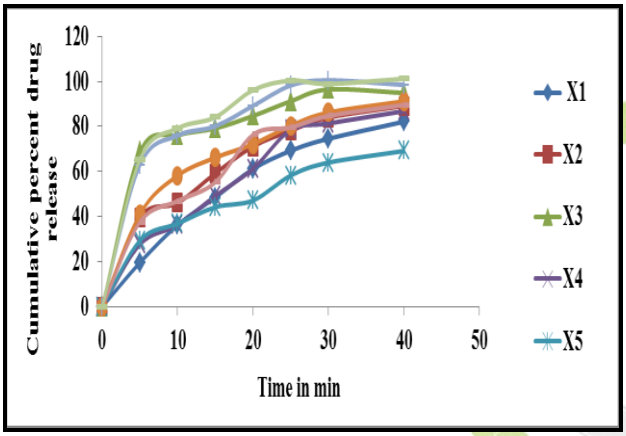

Figure 3: Percent drug release in fast disintegrating liqui - solid and marketed tablets of lamotrigine in 0.1 N HCl

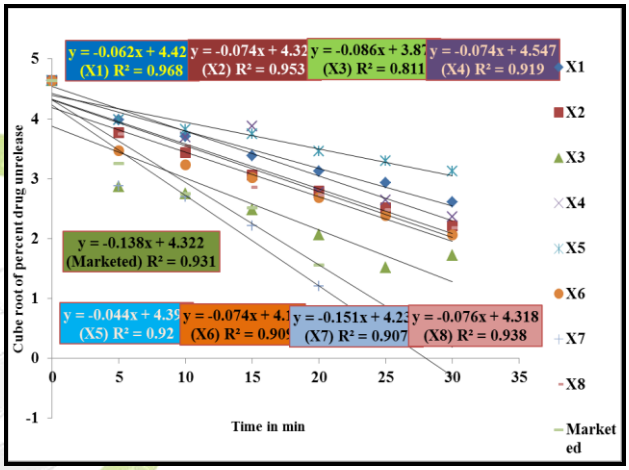

Figure 5: Hixon-crowel dissolution plots of liquid- solid tablets of lamotrigine

Table 8: Dissolution data of lamotrigine liqui solid tablets as per Hixon-crowel cube root law

Time in min	X1	X2	X3	X4	X5	X6	X7	X8	Marketed tablets
5	4.31	3.92	3.15	4.16	4.13	3.59	**3.34**	3.96	3.25
10	3.99	3.77	2.87	3.99	3.98	3.47	**2.88**	3.75	2.75
15	1.19	3.44	2.75	3.7	3.82	3.23	**2.7**	3.54	2.51
20	3.38	3.06	2.48	3.38	3.75	3.02	**2.21**	2.86	1.56
25	3.13	2.79	2.06	2.77	3.46	2.69	**1.2**	2.73	-
30	2.93	2.51	1.52	2.64	3.3	2.39	-	2.48	1.03
40	2.61	2.21	1.72	2.36	3.13	2.06	**0.56**	2.18	-

Application of Kinetic Models

Table 9: Model fitting of the release profile using different models (R^2-value)

Sr. no	Formulation code	Mathematical models (kinetics)		
		Zero order (R^2)	First order (R^2)	Hixon-crowel (R^2)
1)	X1	0.850	0.998	0.968
2)	X2	0.801	0.987	0.953
3)	X3	0.812	0.929	0.811
4)	X4	0.756	0.965	0.919
5)	X5	0.895	0.961	0.92
6)	X6	0.892	0.981	0.909
7)	X7	0.739	0.900	0.907
8)	X8	0.70	0.974	0.938
9)	Marketed	0.715	0.942	0.931

Validation of the Experimental Design

Table 10: Regression equations for the responses

Y1=-2.125+-0.0612A+-0.00625B+0.3225C+3.519AB-2.16AC-2.43BC
Y2=142.5-13A-11.5B+6C+247.5AB+77.5BC+85AC
Y3=15.772-0.08718A-05283B+0.06575C+16.923AB+15.366BC+13.43AC

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

Model Independent Method Formulation (X7) Compared with Marketed Tablet

Table 11: Similarity factor (f_2) and difference factor (f_1) values of liqui solid

Sr. no	Comparison	f_2 value	f_1 value	Dissolution profile
1)	Optimized formulation (X7) and marketed tablet	63.64	10%	Similar

Drug Excipient Compatibility Studies

Drug excipient compatibility studies were carried out by FTIR and the results were given in

- Table FTIR pure drug of lamotrigine results
- Table FTIR liquid- solid formulation results
- Figure IR spectrum of liqui solid formulation results
- Figure IR spectrum of lamotrigine

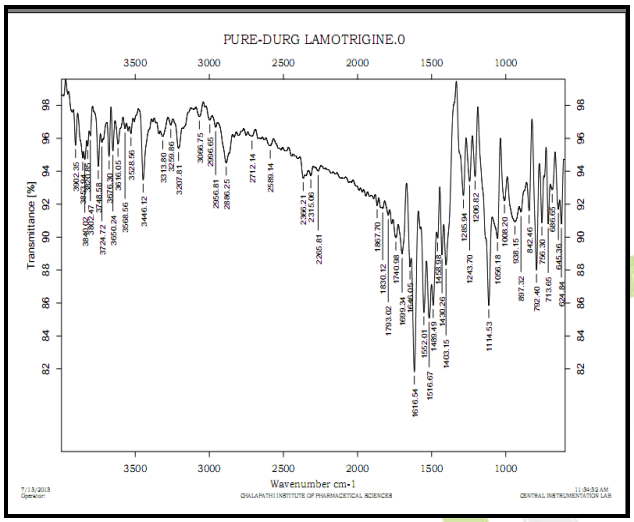

Figure 6: IR spectrum of lamotrigine

Table 12: FTIR pure drug of lamotrigine results

Sr. no	Functional group	IR range	Pure drug of lamotrigine
1)	C-H stretch	3000 - 3100	3066.75
2)	C=C stretch	1400 - 1600	1403.15 - 1552.01
3)	C-C l	600-800	624.84 – 792.40
4)	N-H stretch	3300 - 3500	3313.80 – 3446.12
5)	C=N stretch	2210 - 2280	2265.81

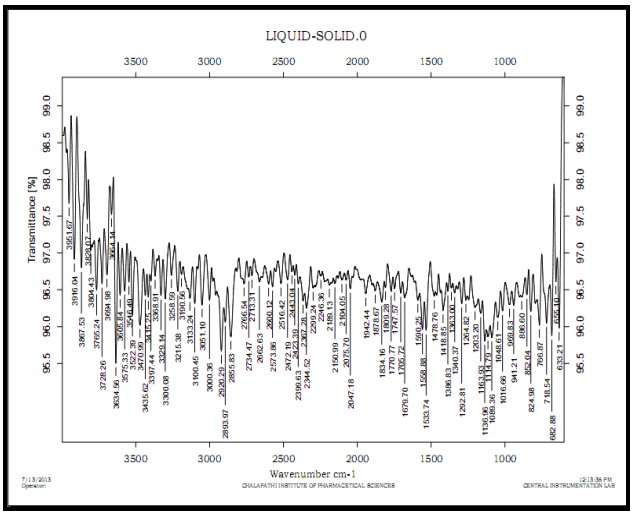

Figure 7: IR spectrum of liqui solid formulation results

Table 13: FTIR liquid- solid formulation results

Sr. no	Functional group	IR range	Liquid-solid formulation (F_4)
1)	C-H stretch	3000 - 3100	3000.36
2)	C=C stretch	1400 - 1600	1418.85 – 1590.25
3)	C-C l	600-800	633.21 – 766.87
4)	N-H stretch	3300 - 3500	3300.36 – 3470.99
5)	C=N stretch	2210 - 2280	2246.36

Table 14: Composition of optimized formulation

Sr. No	Experimental run/Ingredient	X7 (mg)
1	Lamotrigine + carrier & coating materials	100
2	Avicel	40
3	Sodium starch glycolate	10
4	Crosspovidone	0
5	Acacia	20
6	Magnesium stearate	5
7	Talc	5
8	Total tablet weight	180

CONCLUSION

The fast disintegrating tablets of lamotrigine were prepared by liqui-solid technique method using different super disintegrating such as crosspovidone, sodium starch glycolate. Among all formulations containing sodium starch glycolate as super disintegrating is fulfilling all the parameters satisfactorily. Compared to other super disintegrating. The relative efficiency of these super disintegrating to improve the disintegrating and dissolution rates of tablets was in order to sodium starch glycolate > crosspovidone. *In vitro* release studies revealed that almost 90% drug was released from all the formulation were within 30min.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 liquid solid formulation and found to be f2= 63.64 and f1= 10%.Therefore the marketed formulation and liqui solid formulation were similar. Drug excipient compatibility studies were carried out and found no drug excipient interactions

REFERENCES

1. Neligan, A. I. D. A. N., & Sander, J. W. (2009). The incidence and prevalence of epilepsy. *London: UCL Institute of Neurology*.
2. Cohen, A. F., Land, G. S., Breimer, D. D., Yuen, W. C., Winton, C., Peck, A. W. (1987). Lamotrigine, a new anticonvulsant, pharmacokinetics in normal man. *Clinical Pharmaco Therpy, 42,* 535–541.
3. Campellone, J. http://www.cdc.gov/epilepsy/ , 2011.
4. Indurwadenh, N. H., Rajyaguru, T. H., & Nakhat, P. D. (2002). *Fast dissolving tablets*. *39,* 405-409.
5. Nokhodchi, A., Javadzadeh, Y., Siahi-Shadbad, M. R., & Barzegar-Jalali, M. (2005). The effect of type and concentration of vehicles on the dissolution rate of a poorly soluble drug (indomethacin) from liquisolid compacts. *J Pharm Pharm Sci, 8*(1), 18-25.
6. Hentzschel, C. M., Sakmann, A., & Leopold, C. S. (2011). Suitability of various excipients as carrier and coating materials for liquisolid compacts. *Drug Development and Industrial Pharmacy*, *37*(10), 1200-1207.
7. Patel, S. S., Pate, M. S., & Patel, N. M. (2009). Flowability testing of directly compressible excipients accordind to british pharmacopoeia. *Journal of Pharmaceutical Research, 8*, 66-69.
8. Bhowmik, D., Chiranjib, B., Krishnakanth, P., & Chandira, R. M. (2009). Fast dissolving tablet: An overview. *Journal of Chemical and Pharmaceutical Research, 1*(1), 163-177.
9. Mahaveer, P. K. (2010). Orally disintegrating tablets. *International Journal Pharmaceutical Science Bio*, 71-79.
10. Bhowmik, D., Chiranjib, B., Krishnakanth, P., & Chandira, R. M. (2009). Fast dissolving tablet: An overview. *Journal of Chemical and Pharmaceutical Research, 1*(1), 163-177.
11. Panigrahi. R., Behera. S. (2010). Fast Dissolving Tablets. *Webmed central Quality and patient safety* WMC00809, 1-15.
12. Modasiya, M. K. (2009). Design and Characterization of Fast Disintegrating Tablets of Piroxicam. *International Journal of PharmTech Research,* 353-357.
13. Singh, J., Philip, A. K., & Pathak, K. (2008). Optimization studies on design and evaluation of orodispersible pediatric formulation of indomethacin. *AAPS PharmSciTech, 9*(1), 60-66.
14. Bejugam, N. K., Parish, H. J., & Shankar, G. N. (2009). Influence of formulation factors on tablet formulations with liquid permeation enhancer using factorial design. *AAPS PharmSciTech, 10*(4), 1437-1443.

15. Gupta, A. (2010). Recent trends of fast dissolving tablet-An overview of formulation technology. *International Journal of Pharmaceutical & Biological Archive*, *1*(1), 1-10.

16. Goyal, R., Singh B. S., & Pathak, A. (2012). Formulation and evaluation of orodispersible tablets. *World Journal of Pharmaceutical Research, 1*, 576- 590,

17. Brahmanker, D. M, Jaiswal S. B. (1995). *Bioavailability and bioequivalence,* Biopharmaceutics & Pharmacokinetics 1st ed; Vallabh Prakashan, New Delhi, India, 296-302.

18. Karmarkar, B., Indrajeet, D., Avinash, H., Pandurang, N., Dhabale, S. B. (2009). Evaluation of *In –Vitro* Dissolution Profile Comparison Methods. *Latin American Journal of Pharmacy, 28*, 538-43.

19. Karmarkar, B., Indrajeet, D., Avinash, H., Pandurang, N., Dhabale, S. B. (2009). Evaluation of *In –Vitro* Dissolution Profile Comparison Methods. *Latin American Journal of Pharmacy, 28*, 538-43.