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Formulation, optimization and evaluation of fast dissolving tablets of Lamotrigine using natural disintegrant agent

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Abstract---Objective: The present investigative work is aimed for formulating, optimizing and evaluating the Fast Dissolving Tablets (FDT) of Lamotrigine in improving the disintegration time and dissolution rate with Locust bean gum as natural disintegrant agent in combination with Sodium Starch Glycolate (SSG). Methods: Employed 3^2 full factorial design for optimization of Lamotrigine blend formulations. Concentrations of Locust bean gum (X_1) and concentration of SSG (X_2) are two factor independent variables. Experiments are conducted to identify their effect on three dependent variables are disintegration time (Y_1), drug release in 5 min (Y_2), and drug release in 30 min (Y_3). Drug interactions between Lamotrigine and Locust bean gum were investigated with FTIR, DSC, XRD compatibility studies. Direct compression method is used for tablet manufacturing. Results: Pre and post compression parameters of Lamotrigine FDT's are evaluated and found within acceptable limits. Among multiple formulations, LF8 formulation has demonstrated lower disintegration time in 40 ± 3.81sec and wetting time in 38 ± 0.31sec, maximum drug release is 97.88% in 30min. In short time stability studies, no major transformations are identified in physical and chemical properties of Lamotrigine FDT's. In-vivo studies of Lamotrigine fast dissolving tablets showed faster absorption rate. Conclusion: This research study reveals that, the combination with Locust bean gum and Sodium Starch Glycolate has boosted the faster

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dispersion in Lamotrigine drug. Hence, it can be formulated in the manufacturing of FDT's.

***Keywords*---**Drug Release Studies, Fast dissolving Tablets, Lamotrigine, Locust bean gum, Pharmacokinetic Parameters, 3^2Factorial Design.

Introduction

In the global pharmaceutical research and development the fast dissolving tablets are playing a significant role due to its convenience and patient compliance. Different novel and advanced drug delivery systems are introduced in usage of therapeutics. Oral route has gained vital importance for drug administration. In meeting medical emergency needs, the innovators have put efforts to design and develop FDT's by using various natural and synthetic disintegrant agents. FDT's are aimed at investigating different excipients as well as techniques to meet the challenges in formulating and improving the disintegration and dissolution rates of pharmaceutical product (Sehgal et., al 2014).

In the manufacturing of fast dissolving tablets synthetic and natural disintegrant agents play a key role in bringing faster disintegration. Disintegrants causes rapid disintegration because of swelling nature and water absorption by the tablet dose. Natural disintegrants are economical, eco-friendly, abundantly available and non-toxic (Raghavendra & Prasad, 2020). "Locust bean gum is also called as Carob bean gum is a galactomannan vegetable gum extracted from the seeds of the Carob tree (*Ceretonia siliqua*), mostly found in the Mediterranean regions" (Marita & Ana, 2012). It is widely used in food industry as a thickening and gelling agent. Reported that it have bio-adhesive and solubility enhancement properties (Baojie et.,al 2019).

Lamotrigine, an antiepileptic drug belongs to class of Phenyltriazine. Chemically, unrelated to existing antiepileptic drugs. It is used in treatment of partial seizures, depression and bipolar disorder. Lamotrigine has relatively few side effects and do not require blood monitoring in monotherapy. It is a mood stabilizer. "It is rapidly and completely absorbed after oral administration with negligible first-pass metabolism (absolute bioavailability is 98%). Common oral dosage is 25mg per day; belongs to BCS Class II (Low solubility & High permeability). 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 bio availability is because of its low aqueous solubility. (Tarekar & Dave, 2017).
Lamotrigine has selected for this research work to augment the solubility with Locust bean gum as natural disintegrant agent because of its solubility problems; drug needs new techniques to get good bioavailability. In this study, direct compression method employed to formulate the tablets of its multiple advantages like simplest and cost-beneficial for effective methods in preparation of tablets. (Rajeev & Vidyasagar, 2012).

Materials and Methods

Materials

Lamotrigine pure drug is procured from Dr.Reddy's Laboratories (Hyderabad, India). SSG, PVP K30, Talc, Mannitol, and Magnesium stearate Locust bean gum agents are procured from Vijaya Chemicals, Hyderabad. Analytical grade chemicals and reagents were used.

Methods

Standard Graph

To obtain 1000 µg/ml stock solution, 10mg of Lamotrigine drug is dissolved in 10ml of 0.1 N HCL (pH 1.2). By using stock solution prepared different concentrations of 10, 20, 30, 40, 50 (µg/ml). Used 0.1 N HCL (pH 1.2) as a blank solution and found the absorbance at 272 nm (Gunjal et.,al 2019). Constructed and plotted the calibration curve between the Lamotrigine concentration and absorbance is shown at Figure 1.

Optimization by Experimental Design

Complete full factorial design of Two factors, three levels (3^2) is employed as a response surface type of design in order to optimize the prepared preliminary Lamotrigine oral disintegrating tablets, using selected independent variables concentrations of natural disintegrant Locust bean gum (X_1), SSG (X_2). Selected dependent parameters are disintegration time (Y_1), drug release in 5min (Y_2), and drug release in 30min (Y_3) (Gund et.,al 2015). Independent and dependent variables and their coded values as per 3^2 factorial design of fast dissolving tablet of Lamotrigine are shown in Table 1.

Table 1: Coded values as per 3^2 factorial design of Lamotrigine FDTs

Independent Variable	Levels		
	Low (-1)	Middle (0)	High (+1)
Locust bean gum (X_1) (mg)	2	6	10
SSG (X_2) (mg)	2	5	8
Dependent Disintegration Time (sec) (Y_1) % Drug Release in 5min (Y_2) % Drug Release in 30min (Y_3)	Constraint Minimum Maximum Maximum		
Experimental runs	Locust bean gum (X_1)	SSG (X_2)	
1	6	5	
2	6	8	
3	2	5	
4	10	2	
5	2	2	
6	10	5	
7	2	8	

8	6	2
9	10	8

Formulation of Lamotrigine FDTs

Direct Compression method is followed for tablet formulations. Initially, ingredients are properly weighed; pulverized with mortar & pestle then the powdered mass sieved. Before powder punching, added natural disintegrant and Magnesium stearate (Raghavendra & Suresh, 2016). About 80mg mixed powder was condensed into tablets by utilizing Karnavati multiple punch machines and compositions are enlisted in Table 2.

Table 2: Composition of Multiple Lamotrigine FDTs

Ingredients (mg)	LF 1	LF 2	LF 3	LF 4	LF 5	LF 6	LF 7	LF 8	LF 9
Lamotrigine	25	25	25	25	25	25	25	25	25
Locust bean gum	10	2	2	6	10	2	6	10	6
SSG	5	2	8	8	2	5	5	8	2
PVP K 30	10	10	10	10	10	10	10	10	10
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mannitol	47	58	52	48	50	54	51	44	54
Total	100	100	100	100	100	100	100	100	100

These formulations are prepared to study the combined effects of the natural and synthetic disintegrant. So, the optimization was performed to optimize the best blend of the natural disintegrant

Characterization

FTIR Studies
The Spectra of Lamotrigine and powder mixture of optimized drug is recorded on (Perkin Elmer Analyzer by KBr disc method with a scan range of 4,000–400 cm^{-1}.

DSC Studies
Formulation and optimization of pure drug studies were sketched with thermal analysis. 6-8mg of Lamotrigine sample is sealed in aluminum pans, heated at 10^0C /min, in a range of 30 – 300^0C temperature. N_2 gas is used as purging gas at a rate of 40 ml/min. Samples data is analyzed with (DSC- 60, Shimadzu, Japan) and calibrated the temperature and enthalpy scale with Indium standard.

X-ray Diffraction
Diffraction patterns of Lamotrigine and optimized powder mixture was recorded with a Rigaku-D / MAX- 2500 PC Diffractometer.

Pre-compression Parameters
This powdered blend was subjected to test the pre-compression parameters like Bulk Density, Tapped Density, Hausner's Ratio, Carr's Index and Angle of Repose as per the prerequisite guidelines and procedures.

Post Compression Parameters

Drug Content
Selected 10 tablets randomly and powdered with mortar. 10mg of Lamotrigine blend powder was transferred into a 10ml of volumetric flask containing 5ml of methanol and shaken it for 15min and then the methanol was made up to the flask volume. The solution was filtered and dilutions were made to produce 10 µg/ml of Lamotrigine solution, absorbance was measured at 272 nm using UV spectrophotometer and drug content was calculated from the standard calibration curve (Nirmala & Vidyavathi, 2020).

Weight Variation
Selected, randomly 20 tablets from each formulation and individually weighed. Weighed individual tablets are compared for an average weight to calculate the weight variations in tablets.

Thickness
Randomly, selected the tablets from each formulation measured with micrometer screw gauze to determine the thickness of tablets.

Hardness
Monsanto Hardness Tester is used to measure and calculate the average tablets hardness and standard deviation.

Friability
To measure the friability of the Lamotrigine tablets used USP type Roche Friabilator (Pharmalab, Ahmadabad, India). Tablets are weighed and kept in a plastic chamber Friabilator at 25 rpm revolving speed upto 4min. Tablets are re-weighed, dusted and loss of friability percentage is calculated where W1 = initial tablet weight, W2 = final tablet weight

$$Friablity\ (\%) = \frac{W1 - W2}{W1}\ X100$$

Wetting Time
A small petri dish was taken with 10ml of distilled water and placed on a two sides folded tissue paper. Tablet is positioned on a tissue paper and tablet wetting time is noted.

In vitro Disintegration Time
For experimental study of tablet disintegration time (Electrolab, ED-21,) apparatus is used. Six tablets were taken according to pharmacopoeia guidelines (USP 30-NF 25). In each of six tubes of basket containing 0.1 N HCL (pH 1.2) add one tablet and maintain the temperature at 37±1^{o}C. Time taken for disappearance of tablet residue from the disintegration apparatus mesh is noted (Shah et.,al 2009).

In vitro Dissolution Studies
For in vitro drug release studies USP type II dissolution tester (LAB INDIA DS-8000) is utilized. Dissolution of Lamotrigine tablets were conducted in 900 ml of 0.1 N HCL as a dissolution medium with a paddle speed of 50 rpm at 37±0.5 ^{0}C

temperature with time intervals of 0, 5, 10, 15, 20, 25 and 30 min. the dissolution medium was withdrawn and added with fresh medium. In replicates of six dissolution studies were performed under T 60 UV Spectrophotometer (LAB INDIA) a wavelength of 272 nm was used for analysis of the Lamotrigine drug concentration. Calculated the cumulative % of Lamotrigine drug against time and plotted the graph. To fit into different mathematical models the in vitro release values were used.

In vitro Drug Release Kinetics

Constructed multiple kinetic equation models of Zero-Order, First-Order, Higuchi Equation, Korsmeyer-Peppas Equation for in vitro drug release studies (Kolhe & Choudhari, 2014).

Stability Study

Short time stability studies were performed to optimize Lamotrigine fast dissolving tablets. The optimized tablets were packed in aluminum foils and stored in a humidity chamber keeping the temperature at 25 ^{o}C - 40^{o}C and 60% - 75±5% RH for 90 days. Appearance and drug release studies of stored Lamotrigine tablets were identified at the end of every month of storage (Pawar et.,al 2014).

Pharmacokinetics Study

Male Wistar rats (200-250g) were used to carry out the pharmacokinetics studies on Lamotrigine optimized and on marketed formulation. The rats were maintained at a temperature of 20°C ±5°C in clean rooms. To perform in vivo studies obtained animal ethical clearance with vide protocol No.I/IAEC/AGI/004/2020WR. During the pharmacokinetic studies, one day before commencement of studies the rats are fasted and given access to water ad libitum. In this study, rats were grouped into 2 groups (each group have six rats) Group I with the marketed formulation and Group II Lamotrigine optimized fast dissolving tablets. Rats were administered with Fast dissolving tablets dissolved in distilled water in 10 mg/kg (body weight) dose by oral feeding pipe. Retro-orbital bleeding procedure was used for the collection of blood samples from rats at 10, 20, 30 min and at intervals of 1, 2, 3, 4, 6, 8, 10, 12 and 24 h after dosage. For analysis, collected 100 µl of plasma samples and centrifuged with 3000 rpm for 10 min, stored at -20°C. HPLC technique is employed to determine the plasma concentration of Lamotrigine drug. The plasma concentration is applied to develop the plasma profiles by plotting drug concentration-time curves. Residual Method is determined to calculate C_{max}, T_{max}, $t_{½}$, K_e, K_a, AUC_{0-24}, $AUMC_{0-24}$, MRT pharmacokinetic parameters , they are presented as mean ± SD (Zeng et.,al 2013).

Results and Discussion

Standard Graph

Scanning of Lamotrigine drug (200 to 400 nm) in the UV region, the λ_{max} was found at 272 nm. Lamotrigine calibration curve was evolved at 272 nm with 0.1 N HCL (pH 1.2). The regression coefficient of calibration curve R^2 is 0.997.

Calibration Curve vs Absorbance values are given in Table 3 and standard curve is figured in Figure 1.

Table 3: Calibration Curve vs Absorbance

Concentration (µg/ml)	Absorbance
10	0.128
20	0.265
30	0.445
40	0.658
50	0.762

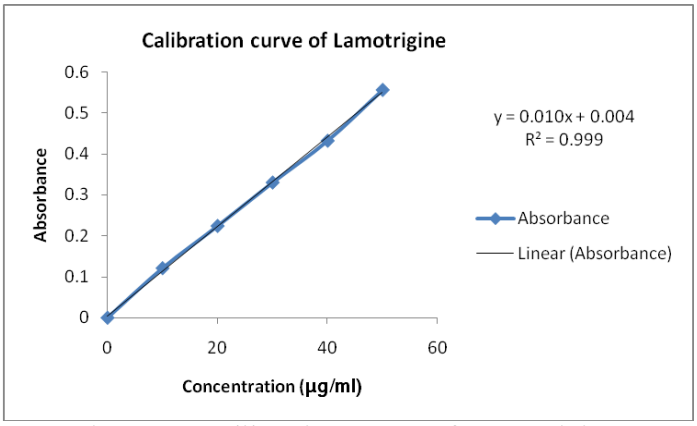


Figure 1: Calibration curve of Lamotrigine

Characterization

FTIR

FTIR spectra of pure Lamotrigine drug displayed characteristic bands stretching and specifying groups at 3385 cm^{-1} is –NH amino, 3203 cm^{-1} is –CH aromatic, 1629 cm^{-1}, 1431 cm^{-1} is C=C ring, 981 cm^{-1} indicates C-Cl of halides all the peaks are indicated in Figure 2.

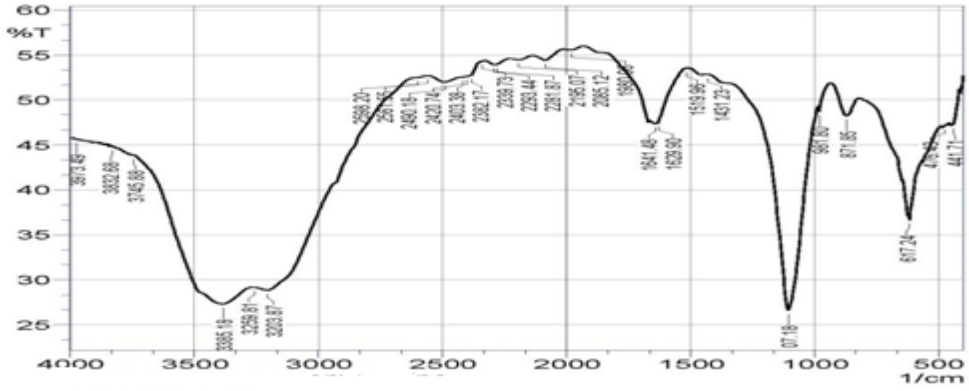


Fig. 2: FT-IR studies of Lamotrigine

FTIR spectra Lamotrigine blend of optimized formulation displayed characteristic absorbance specifying groups at 3421cm^{-1} –NH amino, 3246cm^{-1} –CH aromatic, 1629cm^{-1}, 1462cm^{-1} is C=C ring, 949cm^{-1} indicates C-Cl stretching of halides, all the peaks are shown in Figure 3.

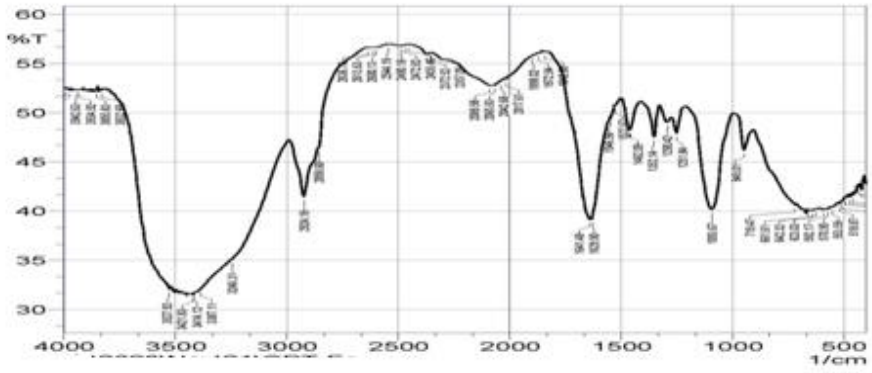


Fig. 3: Lamotrigine optimized formulation (LF8)

IR spectra of optimized formulations indicated all distinguishing peaks of pure Lamotrigine. Hence, resulted no interaction has taken place in between drug and excipient.

DSC

Lamotrigine melting point temperature at 219^{o}C exhibited endothermic peaks. Optimized formulations and pure drug thermographs are revealed in Figures 4 & 5 respectively. It exhibited that there was no disparity among the peaks of Lamotrigine and optimized formulation has revealed the compatibility of with other ingredients.

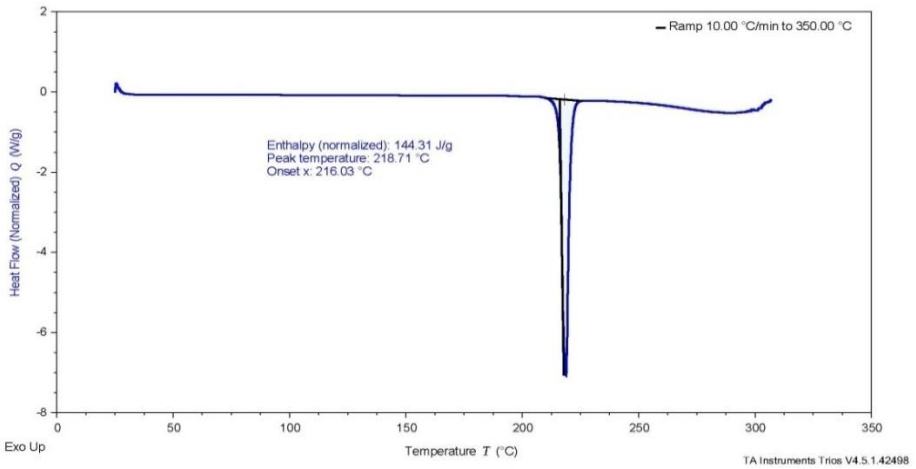


Figure 4: DSC thermogram of Lamotrigine

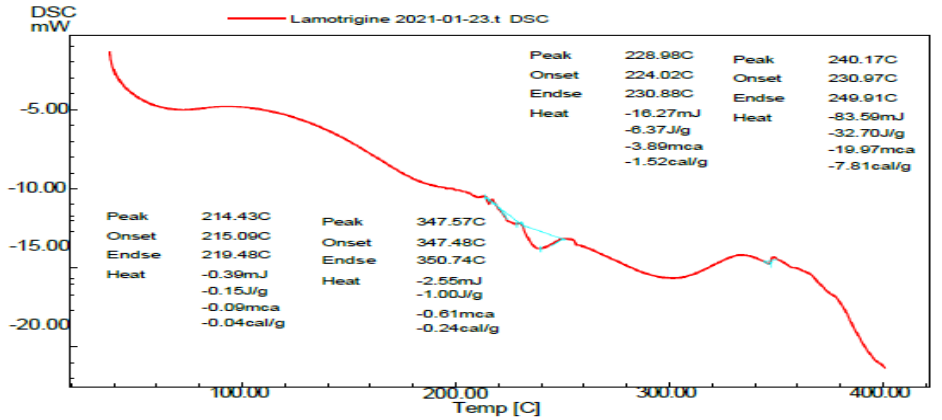


Figure 5: Lamotrigine optimized formulation (LF8)

XRD

Study on degree of crystallinity is performed to identify the XRD pattern of Lamotrigine and optimized formulation as shown in Figures 6 & 7. The crystalline nature is demonstrated by the characteristic sharp intense peaks at 2^{o} in both Lamotrigine and optimized formulation.

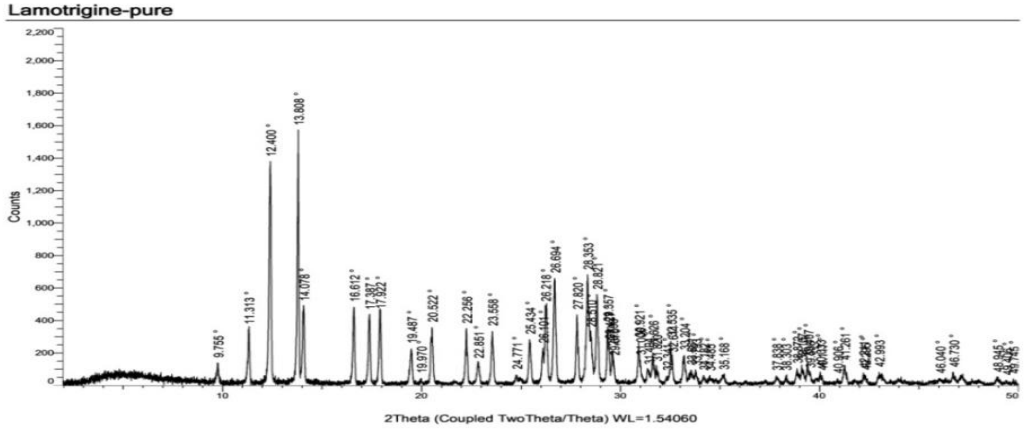


Figure 6: XRD Analysis graphs of pure drug

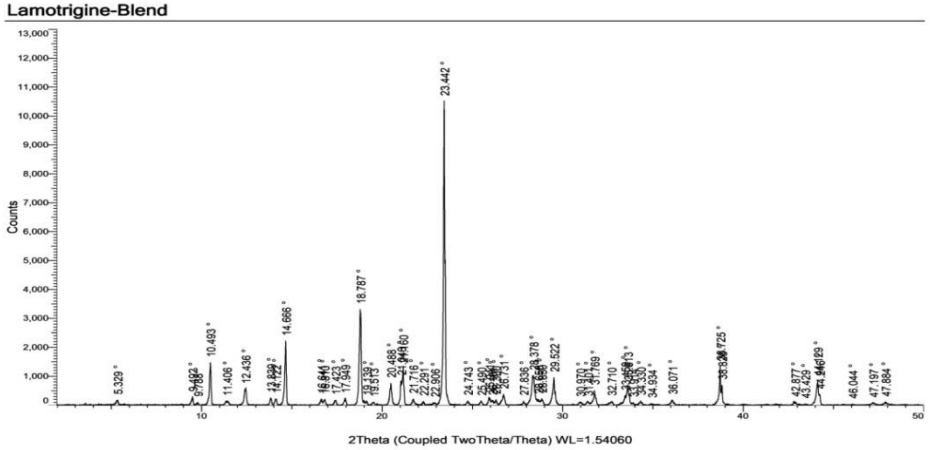


Figure 7: XRD Optimized Formulation (LF8)

Evaluation of Pre-compression Parameters
Evaluated, pre-compression parameters to identify blend flow properties as listed in Table 4.

Table 4: Evaluation of Pre-Compression Parameters

F. No.	Bulk Density	Tapped Density	Compressibility Index	Hausner's Ratio	Angle of Repose (^{0})
LF1	0.352±0.12	0.441±0.23	20.18±0.28	1.25±0.22	29^0
LF2	0.342±0.19	0.452±0.25	24.33±0.30	1.32±0.19	30^0
LF3	0.348±0.21	0.442±0.30	21.26±0.19	1.27±0.22	27^0
LF4	0.35±0.26	0.455±0.28	23.07±0.25	1.30±0.16	30^0
LF5	0.346±0.18	0.452±0.16	23.45±0.21	1.30±0.28	27^0
LF6	0.348±0.22	0.449±0.17	22.49±0.32	1.29±0.30	29^0
LF7	0.352±0.20	0.451±0.18	21.95±0.26	1.28±0.29	30^0
LF8	0.347±0.16	0.453±0.11	23.39±0.22	1.30±0.17	29^0
LF9	0.353±0.11	0.462±0.10	23.26±0.20	1.30±0.19	28^0

Bulk density and tapped density values of various formulations found within the range 0.342 **±** 0.19 to 0.353 **±** 0.02 and 0.441 **±** 0.23 to 0.462 **±** 0.10 respectively. Compressibility Index is in the range of 20.18 **± 0.28** to 24.33 **± 0.30**. Hausener's Ratio was 1.25 **±** 0.22 to 1.32**±** 0.19. Angle of repose is in the range of 27^o - 30^o. All powdered blend formulations revealed the best flow properties in uniform filling while compressing into tablets.

Evaluation of Tablet Properties

In Lamotrigine FDT's, drug contents in all formulations ranged from 97.12%**±**0.29 to 99.32%**±0.31.** Hardness of Lamotrigine tablets showed accepted values of 3.33**±**0.1 to 3.7**±** 0.3 kg/cm^2. In all tablet formulation the friability percentage is less than 1% within 0.24% to 0.36%. Lamotrigine FDT's exhibited uniformity in

weight range from 99.54±0.14 mg to 101.73± 0.08 mg. The thickness was found to be 2.82±0.06 to 2.93±0.10 mm.

Post-compression Parameters
Wetting Time & In vitro Disintegration Time

To determine the competence of disintegrating agents, swelling in water is an essential criterion for wetting time in Lamotrigine FDTs. Wetting time for all Lamotrigine tablets are shown in Table 5. Lamotrigine FDTs optimized formulation LF8 exhibited the least wetting time of 38sec. Disintegration time plays a key role in the different concentrations of natural disintegrant (X_1) and SSG (X_2) led to a pronounced effect in optimization and formulation of FDTs. Disintegration time in FDTs is expressed depending upon the concentrations of X_1 and X_2. Disintegration times for all Lamotrigine FDTs are shown in Table 5 of which LF8 formulation is having the least disintegration time 40 ± 3.81sec. Bar graphs of wetting time and disintegration time are shown in Figure 8.

Table 5: Results of disintegration time and wetting time of prepared FDTs

FDTs Formulation Codes	Wetting Time (Sec) (Sec ± SD)	Disintegration Time (Sec) (Sec ± SD)
LF1	37±0.40	41±0.39
LF2	70±0.30	74±0.42
LF3	43±0.31	48±0.40
LF4	41±0.41	45±0.38
LF5	42±0.39	47±0.41
LF6	53±0.35	58±0.38
LF7	44±0.32	48±0.41
LF8	38±0.31	40±0.38
LF9	47±0.42	52±0.47

(n=3, Mean ± S.D)

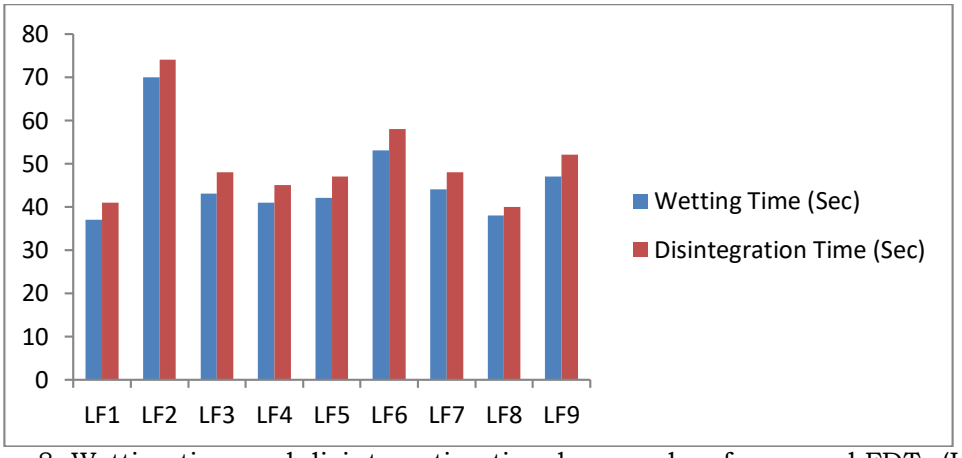


Figure 8: Wetting time and disintegrating time bar graphs of prepared FDTs (LF1-LF9)

The response surface plot demonstrated the effect of amount of disintegrating agents locust bean gum(X_1) and SSG (X_2) on disintegration time. Increased concentrations of X_1 and X_2 exhibited a random effect on disintegration time at low level of disintegrant agents a significant negative effect (increase in disintegration value). 2D and 3D graphs showing the concentration effects of natural disintegrant (X_1) and SSG (X_2) are shown in Figure 9. Disintegration time parameters are described in the following equation

$Y1= 95.29-6.39X_1-6.81X_2+0.39X_1X_2+0.18X_1^2+0.22X_2^2$.

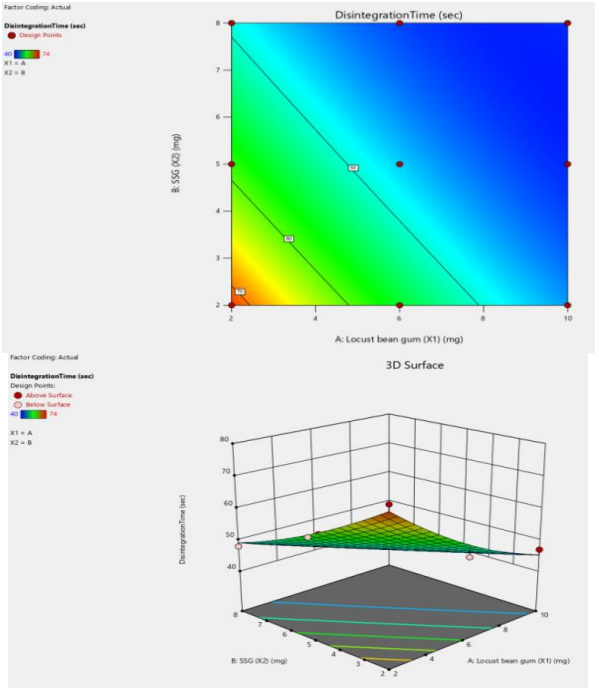


Figure 9: 2D & 3D graphs showing the concentration effects of natural disintegrant (X_1) and SSG (X_2) on disintegration time

In-vitro Dissolution Study

Natural disintegrant (X1) and SSG (X2) showed a significant effect on the drug dissolution in the Lamotrigine ODT formulations Y2 at 5min, Y3 at 30min. Different dissolution study profiles are listed in Table 6. In vitro drug released profiles are prepared for fast dissolving tablets (LF1-LF9) are shown in Figure 10. 2D & 3D graphs showing concentration effect on natural disintegrant (X_1) and SSG (X_2) of drug percentage release after 5min and 30min respectively are shown in Figures 10 and 11.

Table 6: Dissolution studies of Lamotrigine profiles

Time	LF1	LF2	LF3	LF4	LF5	LF6	LF7	LF8	LF9
0	0	0	0	0	0	0	0	0	0
5	28.93±1.84	18.14±1.90	24.58±1.98	27.95±3.20	26.93±2.21	20.14±2.30	25.93±2.52	29.68±1.46	22.14±1.54

10	35.57±2.16	36.25±2.63	35.38±2.30	38.39±2.13	37.12±2.18	38.13±1.46	37.56±1.50	38.12±2.13	37.21±1.24
15	52.35±2.15	50.17±2.14	53.76±1.72	52.27±1.52	53.89±1.56	56.93±1.90	57.81±1.47	59.35±1.47	50.18±1.47
20	70.21±2.13	74.22±3.08	73.91±1.47	71.39±1.30	73.56±2.01	70.13±1.46	75.38±2.01	73.81±1.24	75.56±1.25
25	83.34±2.48	80.45±1.98	81.24±1.91	81.63±1.24	84.31±2.06	82.82±1.25	83.65±2.17	89.74±1.40	90.34±2.17
30	95.63±1.59	91.17±1.85	93.78±2.21	95.82±1.20	94.68±2.2	92.32±2.03	94.58±1.98	97.88±1.19	93.78±1.48

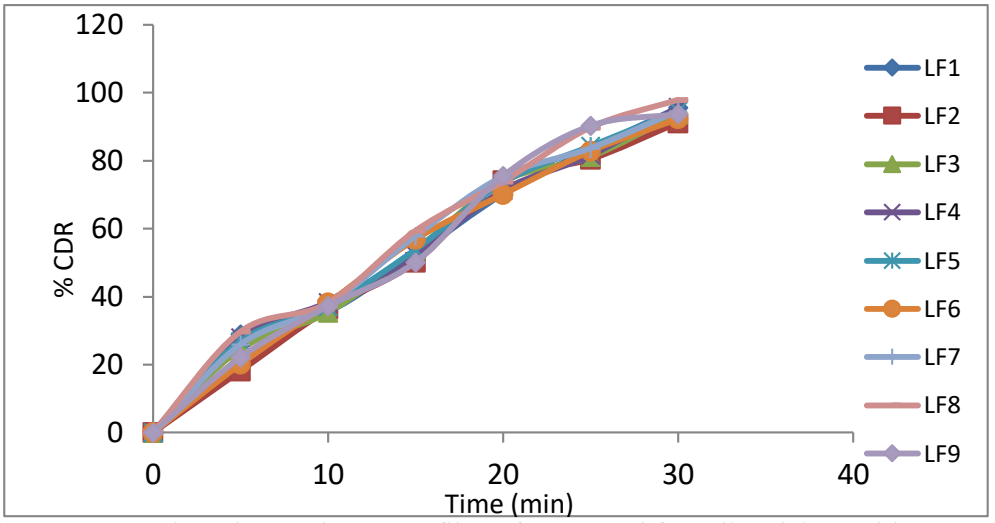


Figure 10: In-vitro drug release profiles of prepared fast dissolving tablets (LF1-LF9)

The response surface plot demonstrated the effect of natural disintegrant agents on CDR, increased concentration of natural disintegrant showed a positive effect on drug release, the parameters of drug release at 5min and 30min are listed in the below equations

$Y_2=11.62+1.78X_1+1.40X_2-0.07X_1X_2-0.03X_1^2-0.01X_2^2$

$Y3=89.81+0.75X_1-0.01X_2+0.01X_1X_2-0.03X_1^2+0.03X_2^2$

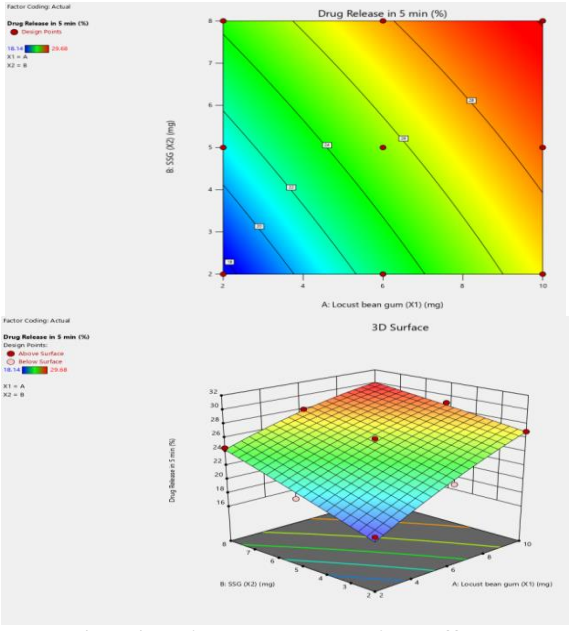


Figure 10: 2D & 3D graphs showing concentration effect on natural disintegrant (X_1) and SSG (X_2) of drug percentage release after 5min

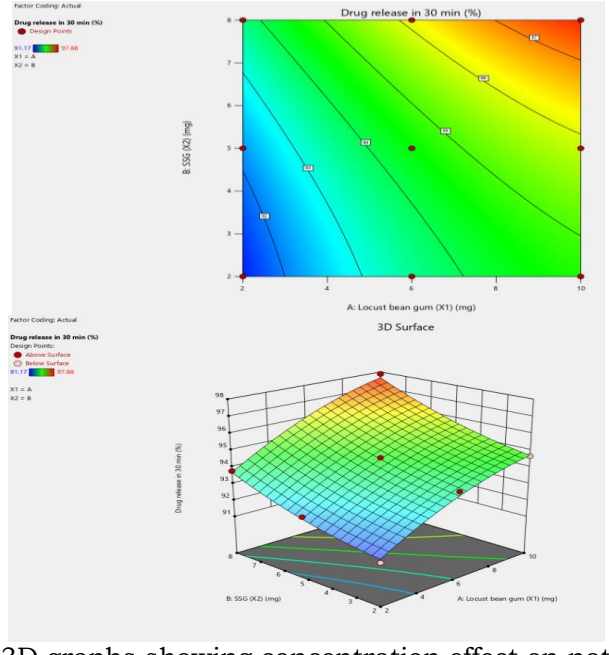


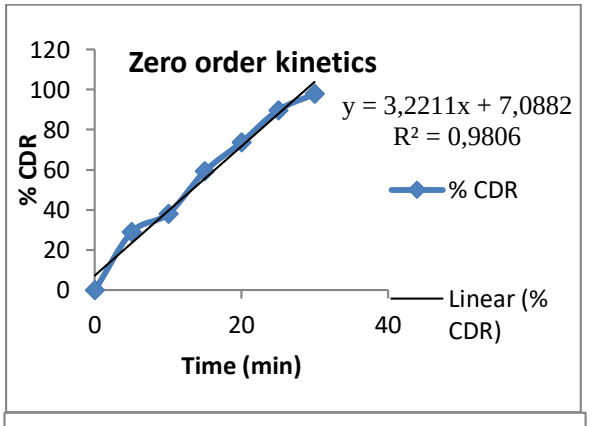
Figure 11: 2D & 3D graphs showing concentration effect on natural disintegrant (X_1) and SSG (X_2) of drug percentage release after 30min

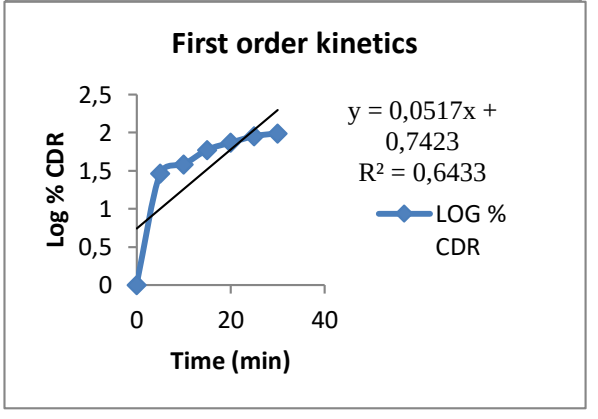
In vitro Drug Release Kinetics

In vitro drug released values Table 7 are instigated and plotted into multiple statistical methods are sown in Figure 12. In Zero-order release kinetics has higher regression values; hence all the Lamotrigine FDTs followed zero order kinetics.

Table 7: In-vitro Drug Release Kinetics

TIME	% CDR	SQUARE T	LOG T	LOG % CDR	ARA	LOG % ARA
0	0	0	0	0	0	0
5	28.93	2.236	0.699	1.46134843	71.1	1.8516863
10	38.12	3.162	1	1.58115289	61.9	1.7915503
15	59.35	3.873	1.176	1.77342072	40.7	1.6090605
20	73.81	4.472	1.301	1.86811521	26.2	1.4181355
25	89.74	5	1.398	1.95298607	10.3	1.0111474
30	97.88	5.477	1.477	1.99069396	2.12	0.3263359





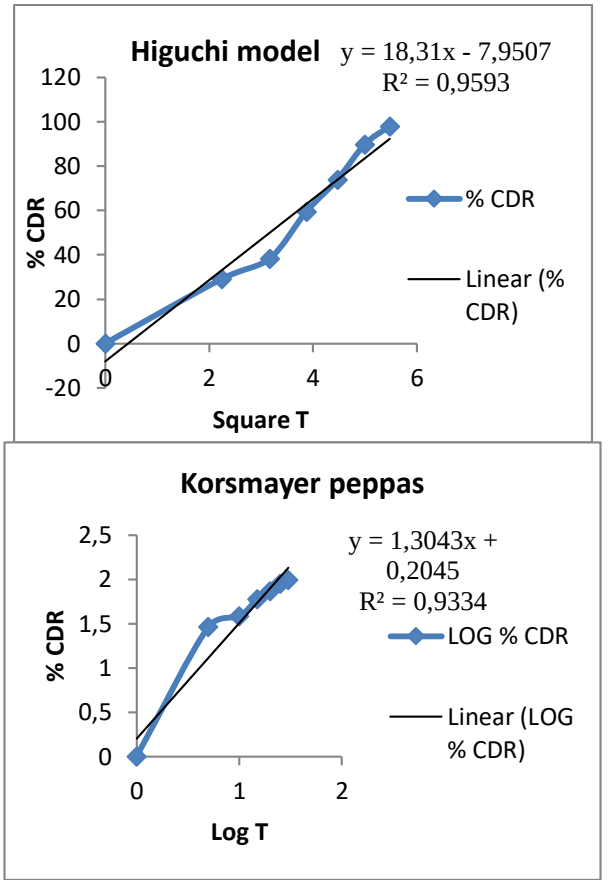


Fig. 12: In-vitro Drug Release Kinetics equation models

Stability studies

No major changes are identified in physical and chemical properties in Lamotrigine FDTs. The short term stability studies data has been projected in Table 8.

Table 8: Stability studies data at different conditions

Optimized formulation	Stability Parameters	0 Month	1st Month	2nd Month	3rd Month	Limits as per Specifications
		In vitro drug release (%)				
LF8	25⁰C/60% RH % Release	97.88±1.19	97.55±2.12	96.74±1.28	95.48±1.25	Not less than 85 %
	30⁰C/75% RH % Release	97.88±1.19	97.46±2.19	96.65±1.29	95.35±1.20	
	40⁰C/75% RH % Release	98.88±1.19	97.35±2.16	96.42±1.32	95.24±1.22	

In vivo Pharmacokinetics Study
HPLC Chromatogram of Lamotrigine and Internal Standard Peaks

The HPLC method was developed and total run time was set to 10min and chromatograms of LMT appeared at 1.47min. The chromatograms of blank plasma, pure LMT in plasma and LMT in mobile phase were shown in Figure 13.

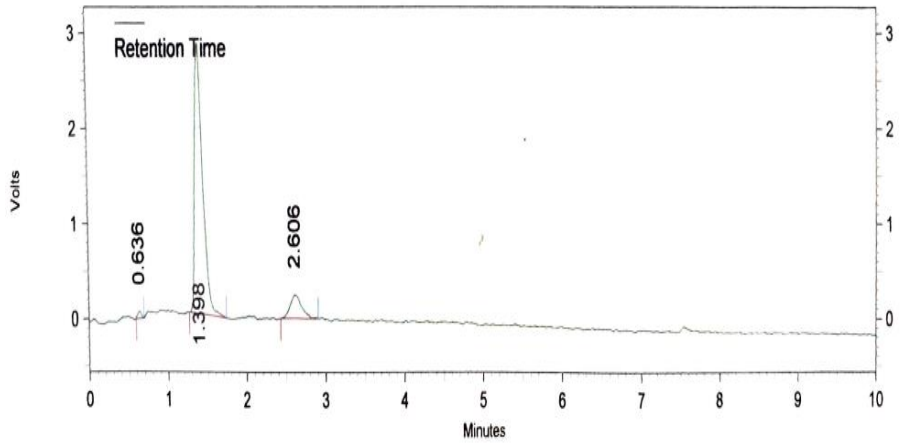


Figure 13: HPLC chromatogram Lamotrigine

The peak area of LMT in mobile phase and plasma was almost similar indicating that there was no interference of any peaks with the drug peak. Standard curve was plotted between peak area and concentration in Table 9 and is shown in Figure 14. A better relationship in linearity was observed with a high R^2 =0. 9991

Table 9: Standard curve data for Lamotrigine in rat plasma

Sl no.	Concentration (µg/ml)	Peak area
1	2	200
2	4	424
3	6	715
4	8	978
5	10	1204
6	12	1535
7	14	1831

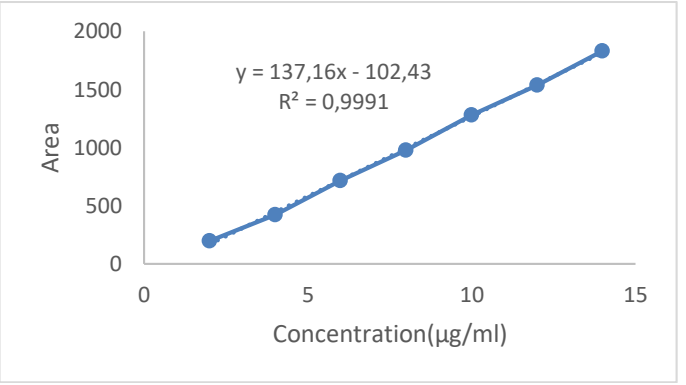


Figure 14: Standard curve of Lamotrigine in rat plasma

The mean maximum plasma concentrations (C_{max}) of the developed for optimized Lamotrigine formulation were higher than the marketed tablets. The higher AUC value of optimized formulation refers to higher bioavailability as compared to marketed Lamotrigine. The pharmacokinetic parameters are defined in Table 10 and plotted the curve in Figure 15.

Table 10: Pharmacokinetic parameters of ND- LMT and Marketed LMT FDTs

Pharmacokinetic Parameters	Optimized Lamotrigine FDT	Marketed Lamotrigine Tablodep 5mg)
$t_{1/2}$ (hr)	24.32±0.27	24.34±0.31
C_{max} (µg/ml)	230.47±0.22	98.11±0.42
T_{max} (hr)	0.8	1
K_e (h^{-1})	0.0284	0.0284
K_a (h^{-1})	1.98	0.36
AUC_{0-24} (µg/ml. h)	1676.01±0.22	720.56±0.31
$AUMC_{0-24}$(µg/ml. h^2)	10286±0.08	4023.44±0.24
MRT(hr)	6.137189	5.583

(Mean±SD, n=6)

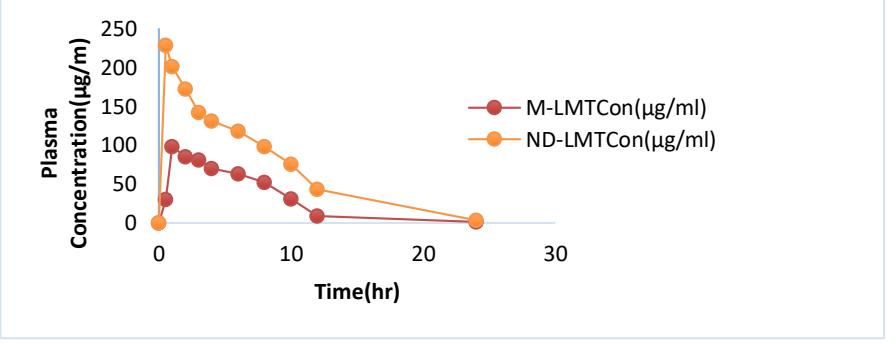


Figure 15: In vivo Plasma concentration graph of Marketed Lamotrigne (M-LMT) and Optimized Lamotrigine (ND-LMT) FDTs

Conclusion

This study concludes that formulations of Lamotrigine FDTs are prepared to study the combined effects of Locust bean gum (natural disintegrant) in combination with that of SSG (synthetic disintegrant). 3^2 full factorial design is employed for formulations and optimization of Lamotrigine FDTs. The selection of an ideal batch of FDTs is considered after evaluating the parameters like disintegration time, wetting time and dissolution studies. LF8 batch FDTs are identified as the finest formulation among all formulations. It showed best results in disintegration time, dissolution studies and wetting time. It illustrated maximum cumulative in vitro drug release percentage is 97.88. The mean maximum plasma concentration (C_{max}) of the developed Lamotrigine ODT (LF8) is higher than the marketed tablets. The higher AUC value of Lamotrigine ODT refers to higher bioavailability as compared to marketed Lamotrigine. Locust gum bean powder was found to be a natural disintegrant in formulating the Lamotrigine FDTs to release the drug immediately.

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