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Research

Formulation and invitro characterization of lamotrigine fast dissolving tablets by solid dispersion technique

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Abstract

An antiepileptic drug called lamotrigine is a phenyl triazine antiepileptic used to treat some types of epilepsy and bipolar I disorder. It is a medication of BCS class II with a longer half-life. Lamotrigine solid dispersion with oral disintegrating tablet was created using Xylitol, Sorbitol, and SSG to enhance biological performance. Lamotrigine solid dispersions were created using several carriers at various drug and carrier ratios (1:1, 1:2and1:3). Results of solid Lamotrigine dispersions made using the solvent evaporation method, including solubility, melting point analysis, drug content homogeneity, and in vitro dissolution experiments, were discussed. Numerous analytical methods, including FT-IR studies, were used for solid-state characterization. The formulation (F6) combining lamotrigine + SSG (1:3) exhibits better results by solvent evaporation method at the end of 60 min with maximum drug release, hence it was chosen as the best formulation in the end by comparing all of the formulations. The Fast-dissolving tablets were created from the optimal formulation employing various disintegrants at various concentrations. The parameters for pre- and post-compression were examined, and the findings were presented. All findings fall within the allowed range. Using a buffer with a pH of 0.1N, the in vitro drug release of the prepared tablets was carried out. PEG-4000-containing formulation F6C6 demonstrates 99.87% drug release in 20 minutes. First order release kinetics is followed by the improved formulation.

Keywords: Lamotrigine, Xylitol, Sorbitol, Sodium Starch Glycolate, FTIR.

INTRODUCTION

Swallowing can be a problematic problem in cases of dysphasia, particularly in children and the elderly. The pharmaceutical industry now has a new standard thanks to oral disintegrating pills. ODT was commonly replaced with porosity pills, Rapi melts, Oral dissolvable tablets, mouth-dissolving tablets, Rapid disintegrating tablets, fast dissolving tablets, and melt-in-mouth tablets. [1]

Within in 1 minute, they quickly dissolve in the oral cavity. [2,3,4] They were created using different methods, and the resulting ODTs exhibit variations in their sensory qualities, like mouth feel, swallowability, and flavour.

They also display changes in the functionality of the product, including tablet mechanical strength, drug release, bioavailability, and stability. Mass extrusion, spray drying, the cotton candy process, lyophilization, molding, compaction (wet & dry granulation, direct compression), and proprietary technologies (Durasolv®, Orosolv®) are some of the manufacturing processes used to create ODTs. [5,6,7.]

Lamotrigine, a medication used to treat epilepsy, is licensed in the United States for the treatment of bipolar disorder and partial seizures.

It is classified as a class-II drug by the BCS and has a 98% oral bioavailability rate.

It is offered in the market in formulations for both immediate release and sustained release, with dosages ranging from 25 mg to 100 mg. Lamotrigine (Lamictal-ER) extended release was approved by the FDA for GSK in 2009.XR). [8,9,10,11,12,13,14]

Due to several benefits, including the easiest and most affordable tablet production technique, the direct compression method was used to make tablets in the current study inquiry. [15]

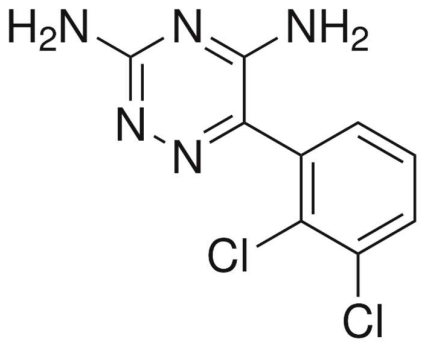

Fig 1: Structure of Lamotrigine

MATERIALS & METHODS

LAMOTRIGINE API was procured from B.M.R. Chemicals, Xylitol, Sorbitol, Mannitol, PEG-4000 was procured from S.D FINE CHEMICALS, and Sodium starch glycolate, Micro crystalline cellulose, Magnesium stearate, Talc was procured from B.M.R. Chemicals, Hyderabad.

Preparation of solid dispersions of lamotrigine

There are several carriers that have been described for the manufacture of solid dispersions employing different methods involving sorbitol, xylitol, and SSG.

Solvent evaporation

The drug and carriers were combined in 1:1, 1:2, and 1:3 ratios in ethanol for the solvent evaporation technique. Solvent was eliminated through evaporation at a low pressure. The bulk was ground up and sent through sieve #60. The finished object was now assembled.

FORMULATION CODE	DRUG: POLYMER RATIO (LAMOTRIGINE: XYLITOL)
F1	1:1
F2	1:2
F3	1:3

FORMULATION CODE	DRUG: POLYMER RATIO (LAMOTRIGINE: SORBITOL)
F4	1:1
F5	1:2
F6	1:3

FORMULATION CODE	DRUG: POLYMER RATIO (LAMOTRIGINE: SODIUM STARCH GLYCOATE)
F7	1:1
F8	1:2

F9	1:3

Evaluation of Solid Dispersions

Prepared polymer drug conjugates were evaluated by

1) Estimation of drug content
2) *In- vitro* dissolution studies

Estimation of Drug Content

A quantity that was precisely measured and transferred to a 100 ml volumetric flask was equal to 5 mg of the medication. To guarantee the full solubility of the drug, the volume was then made up with a 0.1N HCL pH buffer and agitated for 10 minutes. After that, the remedy was filtered. By dissolving 5 mg of the standard medication in a 0.1N HCL, the same concentration of the standard solution was created. Lamotrigine's absorbance was measured in a UV-visible spectrophotometer at 269 nm for both the sample and the standard solutions.

In vitro dissolution study

A capsule containing the generated solid dispersions and 5 mg of Lamotrigine weight equivalent was then subjected to in vitro disintegration. USP type 2 paddle methods were used in the dissolution test (apparatus II). 0.1N HCL buffer was utilized as the dissolution medium, and the solution medium was maintained at 37 0.5 °C. The stirring speed was 50 rpm. Using a UV-visible spectrophotometer, samples of 5 ml were taken out at regular intervals, filtered, and replaced with 5 ml of fresh dissolution medium. Dilutions were made as needed, and the presence of Lamotrigine was then determined at 304 nm.

Kinetics of drug release

The mechanism of drug release for the Lamotrigine solid dispersions was determined using zero order and first order.

The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows: -

1. Zero – order kinetic model – Cumulative % drug released versus time.
2. First – order kinetic model – Log cumulative percent drug remaining versus time.

Formulation of lamotrigine tablets

Equivalent weight of Lamotrigine was added with suitable excipients and the tablets were formulated by direct compression according to the formulae given in the table.

All the ingredients were passed through # 40 mesh sieve separately. The drug and MCC were mixed by adding small portion of each at a time and blending it to get a uniform mixture and kept aside.

Then the other ingredients were mixed in geometrical order and passed through coarse sieve (#40 mesh) and the tablets were compressed using hydraulic press. Compression force of the machine was adjusted to obtain the hardness in the range of 3-4 kg/cm^2 for all batches. The weight of the tablets was kept constant for all formulations F9C1to F9C6.

Table 1: Formulation of Lamotrigine Solid Dispersion Tablet

INGREDIENTS (MG)	F6C1	F6C2	F6C3	F6C4	F6C5	F6C6
Lamotrigine (Equivalent To 100mg)	400	400	400	400	400	400
Mannitol	24	48	72	--	--	--
Peg-4000	--	--	--	24	48	72
MCC	QS	QS	QS	QS	QS	QS
Mg.st	16	16	16	16	16	16
Talc	8	8	8	8	8	8
Total	600	600	600	600	600	600

Precompression Parameters

Method Preparation of Mixed Blend of Drug and Excipients

All the materials were passed through sieve no. 80. Required quantity of each ingredient was taken for each specified formulation (Mentioned in Table) and all the ingredients were subjected to grinding to a required degree of fineness (except magnesium stearate and talc). The powdered blend was evaluated for flow properties as follows.

Angle of repose

Angle of repose is determined by using funnel method. The accurately weighed blend is taken in a funnel. The height of the funnel is adjusted in such a way that the tip of the funnel just touches the apex of the heap of blend. The drug-excipient blend is allowed to flow through the funnel freely on to the surface. The diameter of the powder cone is measured and angle of repose is calculated using the following equation. Angle of Repose less than 30 ° shows the free flowing of the material.

$$\theta = \tan^{-1} (h / r)$$

Bulk density

Apparent bulk density is determined by pouring a weighed quantity of blend into graduated cylinder and measuring the volume and weight. The bulk density was calculated by using the below mentioned formula

$$D_b = \frac{M}{V_o}$$

Where,

M is the mass of powder, **V0** is the bulk volume of the powder

Tapped density

It is determined by placing a graduated cylinder, containing a known mass of drug-excipients blend. The cylinder is allowed to fall under its own weight onto a hard surface from the height of 10 cm at 2 second intervals. The tapping is continued until no further change in volume is noted.

The tapped density was calculated using the following formula,

$$D_T = \frac{M}{V_t}$$

Where,

M is the mass of powder, V_T is the tapped volume of the powder

Compressibility index

The simplest way for measurement of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index(I) which is calculated as follows,

Carr's Index (I) = (Tapped Density-Bulk Density)/(Tapped Density) x100

The value between 13-19% indicates a powder with usually good flow characteristics, whereas above 21% indicate poor flowability.

Hausner's Ratio

Hausner, s ratio is an indirect index of ease of powder flow. It is calculated by the following formula

$$\text{Hausner's Ratio} = \frac{\text{BulkDensity}}{\text{TappedDensity}}$$

Where D_t is tapped density and D_b is bulk density

Lower Hausner's ratio (<1.25) indicates better flow properties and higher Hauser's ratio (>1.25) indicates poor flow properties.

Evaluation of tablets

Post compression parameters

Weight variation test

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. First the total weight of 20 tablets from each formulation is determined and the average is calculated. The individual weight of the each tablet is also determined to find out the weight variation.

Tablet hardness

The hardness of tablet is an indication of its strength. It is the force required to break a tablet by compression in the radial direction. The force is measured in kg and the hardness of about 3-5 kg/cm^2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation is determined by Monsanto hardness tester, Pfizer hardness tester etc. Excessive hardness significantly reduces the disintegration time.

Tablet friability

Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling and transport. Roche friabilator is employed for finding the friability of the tablets. Weigh the 20 tablets from each batch and place in Roche friabilator that will rotate at 25 rpm for 4 minutes. All the tablets are dedusted and weighed again. The percentage of friability can be calculated using the formula.

$$\% \text{ Friability} = [(W1-W2)100]/W1$$

Where,

W1= Weight of tablet before test, W2 = Weight of tablet after test

In-Vitro Disintegration time

Tablet disintegration is an important step in drug absorption. The test for disintegration was carried out in Electrolab USP disintegration test apparatus. It consists of 6 glass tubes which are 3 inches long, open at the top, and held against a 10-mesh screen, at the bottom end of the basket rack assembly. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 liter beaker containing pH 0.1N HCL buffer solution at 37°C ± 1°C such that the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted.

Thickness and Diameter

Tablet thickness and diameter can be measured using a simple procedure. Five tablets are taken and their thickness is measured using Vernier calipers. The thickness and diameter is measured by placing tablet between two arms of the Vernier calipers.

Drug content uniformity

The tablets were tested for their drug content uniformity. At random 20 tablets were weighed and powdered. The powder equivalent to 5 mg was weighed accurately and dissolved in 100ml of 6.8pH phosphate buffer. The solution was shaken thoroughly. The undissolved matter was removed by filtration through Whatman No.41 filter paper. Then the dilute the solution to obtain 10µg solution. The absorbance of the diluted solutions was measured at 275 nm.

Dissolution studies

In-vitro dissolution study is performed by using USP Type II Apparatus (Paddle type) at 50 rpm. 0.1N HCL buffer 900 ml is used as dissolution medium which is maintained at 37±0.5°C. Aliquots of dissolution medium (5 ml) are withdrawn at specific time intervals and filter. An equal amount of fresh dissolution medium is replaced immediately following withdrawal of test sample. The percentage of drug released at various intervals is calculated using beer-lamberts law.

Kinetics of drug release

The mechanism of drug release for the Lamotrigine solid dispersions was determined using zero order and first order.
The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows: -

1. Zero – order kinetic model – Cumulative % drug released versus time.
2. First – order kinetic model – Log cumulative percent drug remaining versus time.

Zero Order Kinetic

It describes the system in which the drug release rate is independent of its concentration.
Qt = Qo + Ko t

First Order Kinetic

It describes the drug release from the systems in which the release rate is concentration dependent.
Log Qt = log Qo + kt/ 2.303

RESULTS AND DISUSSIONS

Solubility

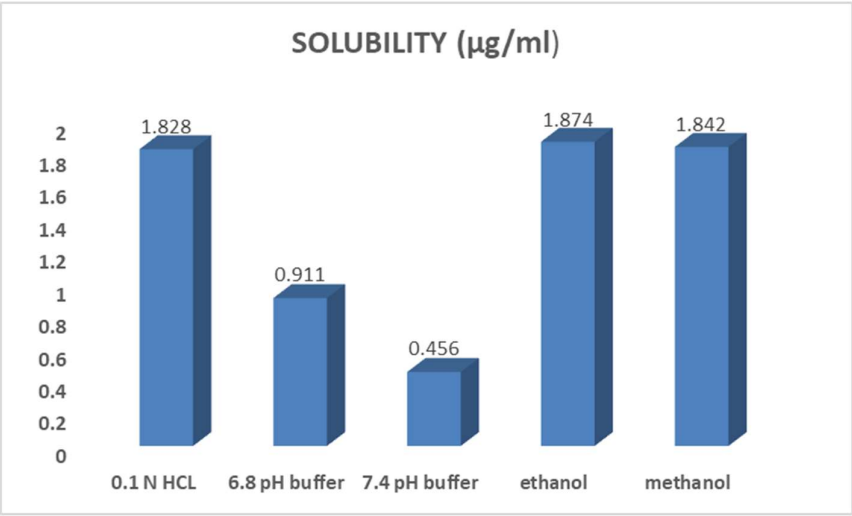

Fig 2: Graphical representation of Lamotrigine Solubility studies

From the above conducted solubility studies in various buffers we can say that 0.1N HCL Buffer solution has more solubility when compared to other buffer solutions.

Analytical method development by U.V. Spectroscopy

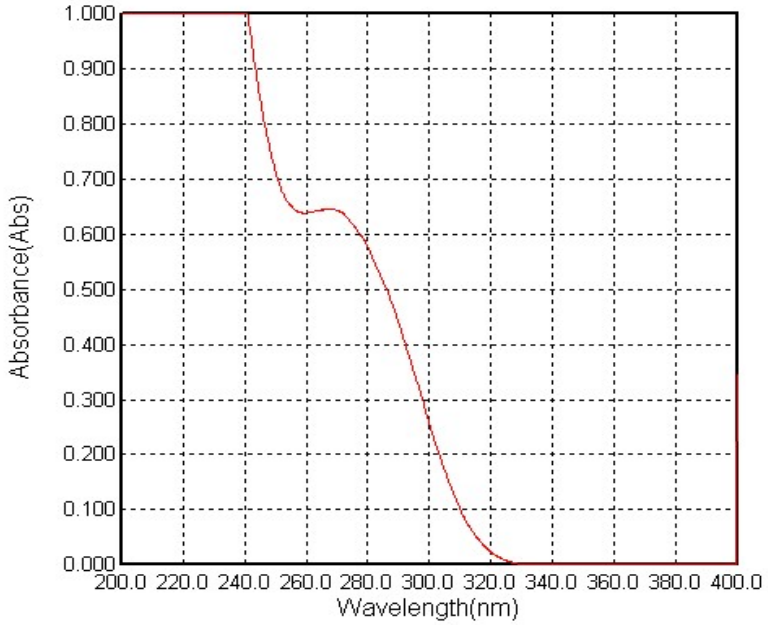

Fig 3: UV Scan Spectrum of Lamotrigine:

Lamotrigine at 10µg/ml was found to be 269 nm.

Calibration curve data of Lamotrigine

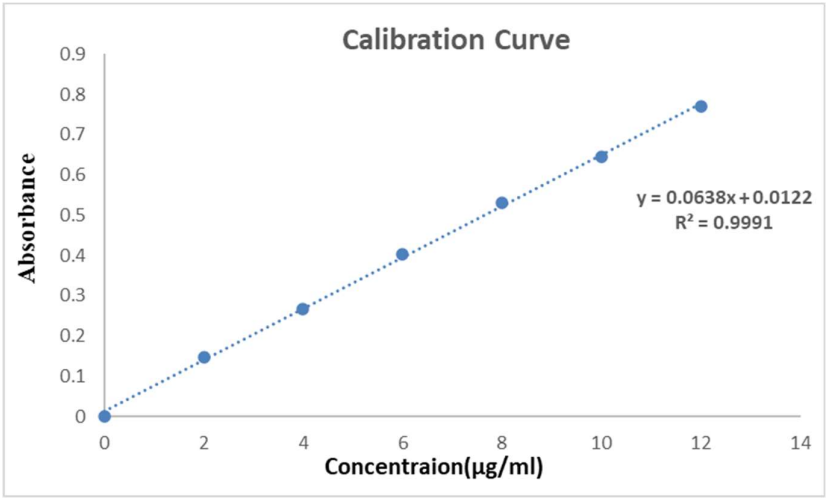

Fig 4: Calibration curve of Lamotrigine

Drug excipient compatibility

Drug and excipient compatibility was confirmed by comparing spectra of FT-IR analysis of pure drug with that of various excipients used in the formulation.

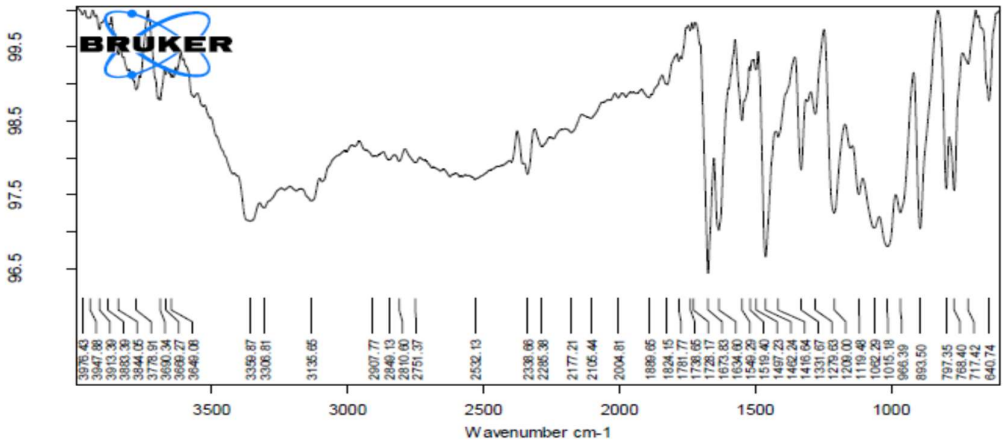

Fig 5: IR spectrum of pure Lamotrigine

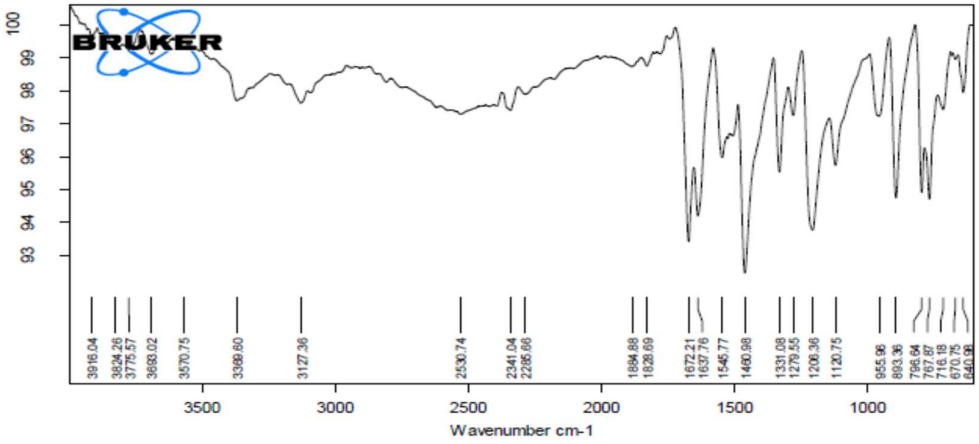

Fig 6: IR spectrum of Lamotrigine Optimized Formulation

Percentage yield of solid dispersions

Table 2: Percentage yield of solid dispersions

Formulation code	Percentage yield
F1	92.12
F2	94.40
F3	95.59
F4	96.10
F5	91.12
F6	98.38
F7	97.65
F8	94.67
F9	96.86

Discussion: The Percentage yield of the formulated solid dispersions was found to be in the range of 91.12% - 98.38% respectively.

Percentage drug content of solid dispersions

Table 3: Percentage drug content of solid dispersions

Formulation code	%Drug content
F1	97.12

F2	98.80
F3	95.54
F4	91.19
F5	93.36
F6	98.82
F7	93.17
F8	95.78
F9	97.14

The percentage Drug content of the formulated solid dispersions was found to be in the range of 91.19- 98.82% respectively

Invitro drug release studies of solid dispersions

Table 4: *Invitro* drug release studies for formulations (F1-F9)

Time (Min)	Percentage drug release								
	Lamotrigine: Xylitol			Lamotrigine: SSG			Lamotrigine: Sorbitol		
	1:1 (F1)	1:2(F2)	1:3 (F3)	1:1 (F4)	1:2 (F5)	1:3(F6)	1:1(F7)	1:2(F8)	1:3(F9)
0	0	0	0	0	0	0	0	0	0
5	36.54	41.52	43.15	32.35	38.75	**57.75**	41.26	42.18	35.17
10	47.19	50.75	57.75	42.86	44.85	**62.78**	48.25	56.75	48.25
15	54.87	59.52	69.55	49.96	55.75	**69.25**	59.13	60.51	54.36
30	68.58	63.51	75.97	58.70	62.96	**74.78**	64.39	68.86	66.14
45	72.82	76.45	84.25	67.82	65.18	**89.15**	76.15	78.66	69.32
60	87.78	88.75	93.18	72.82	79.75	**98.82**	85.78	85.96	84.85

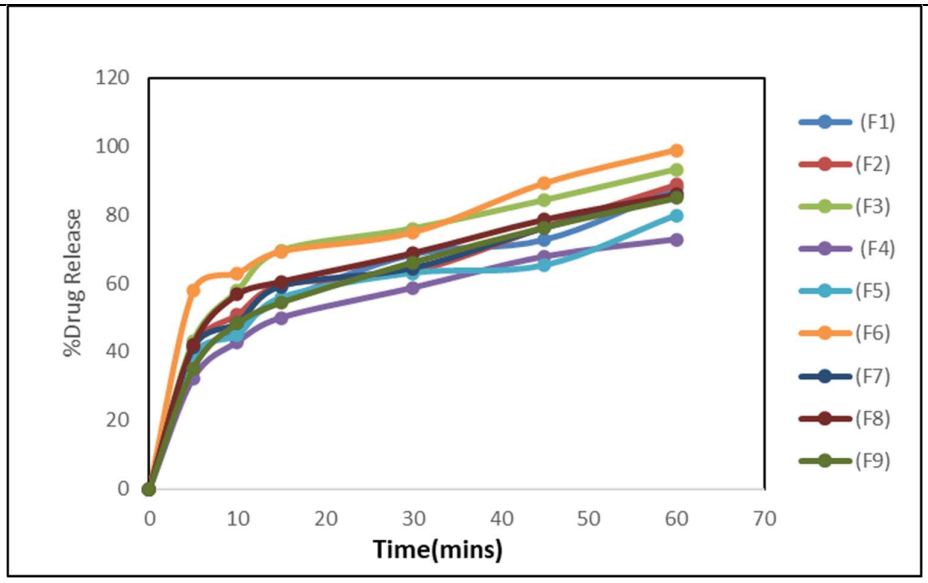

Fig 7: *Invitro* drug release profile for (F1-F9)

In-vitro drug release kinetics studies for best formulation F6
Zero order release kinetics studies

Fig 8: Zero order release profile for best formulation (F6)

First order release kinetics studies

Fig 9: First order release profile for best formulation (F6)

Evaluation of Lamotrigine Fast disintegrating Tablets

Table 5: Pre-Compression parameters

Formulation Code	Derived properties		Flow properties		
	Bulk density (mean ± SD)	Tapped density (mean ± SD)	Angle of repose (mean ± SD)	Carr's index (mean ± SD)	Hausner's ratio (mean ± SD)
F6C1	0.318	0.382	22.64	13.36	1.34
F6C2	0.367	0.356	24.48	14.24	1.30
F6C3	0.386	0.398	25.34	13.12	1.34
F6C4	0.345	0.378	32.12	14.56	1.38
F6C5	0.368	0.396	28.37	12.61	1.24
F6C6	0.385	0.378	26.68	14.39	1.40

Characterization of tablets

Post Compression parameters

All the batches of tablet formulations were characterized for official evaluation parameters like Weight variation, Hardness, Friability, Tablet thickness and drug content and results are shown in the table.

Table 6: Characterization Lamotrigine Fast disintegrating tablets

Formulation	Weight variation (mg)	Thickness (mm)	Diameter (mm)	Hardness (kp)	Friability (%)	Disintegrating time(sec)	Drug content (%)
F6C1	600.17	3.24	8.21	3.4	0.56	20	99.89
F6C2	598.26	3.15	8.36	3.6	0.13	24	97.32
F6C3	599.12	3.07	8.48	3.5	0.34	15	96.17
F6C4	600.43	2.98	8.32	3.7	0.67	30	99.25
F6C5	599.78	3.36	8.24	3.8	0.78	14	100.78
F6C6	600.56	3.24	8.76	4.0	0.95	22	99.55

Dissolution studies of the tablets

The prepared tablets were subjected to dissolution studies in order to know the amount drug release.

Table 7: % Cumulative drug release of formulations F9C1 – F9C6

Time (Min)	F6C1	F6C2	F6C3	F6C4	F6C5	F6C6
0	0	0	0	0	0	**0**
5	50.38	61.36	58.21	62.28	65.57	**81.78**
10	59.06	68.87	85.78	74.23	78.65	**89.14**
15	67.24	74.23	92.92	81.23	84.63	**95.25**
20	74.15	84.26	96.23	88.42	90.15	**99.87**
25	84.54	92.78	99.88	92.35	96.74	
30	92.35	99.14		99.35		

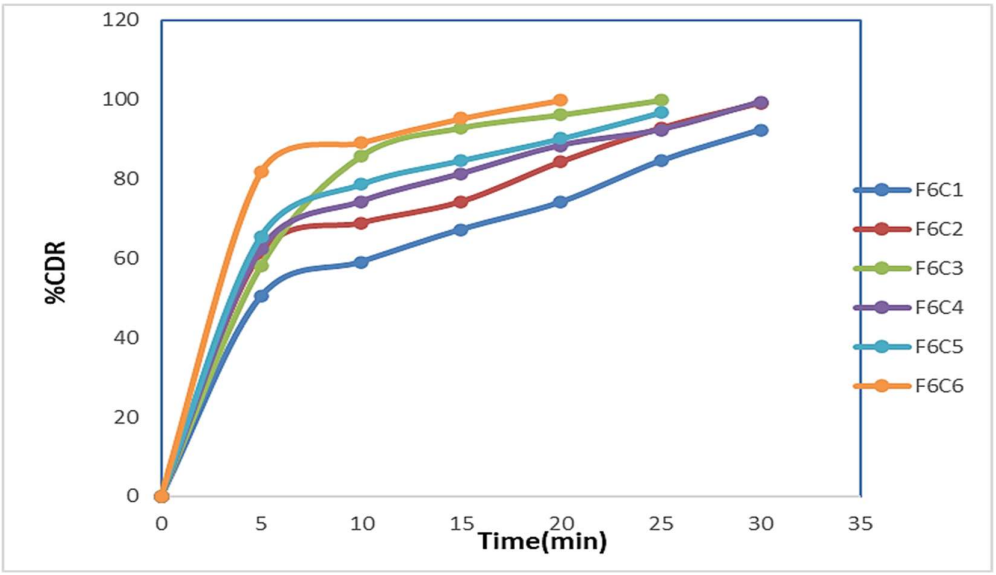

Fig 10: In vitro drug release of formulations F6C1-F6C6

Drug release kinetics
Zero order plot of (F6C6)

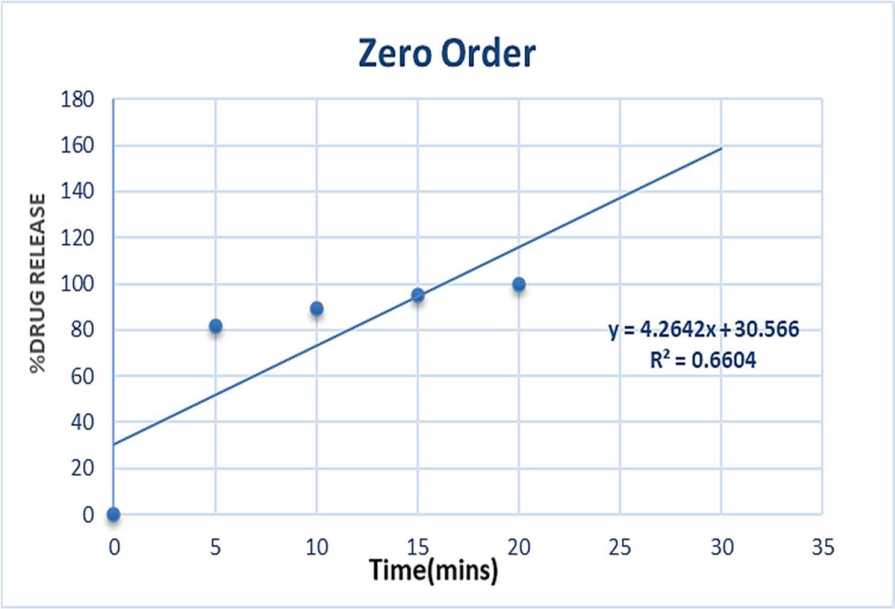

Fig 11: Zero order plot of (F6C6)

First order plot of (f6c6)

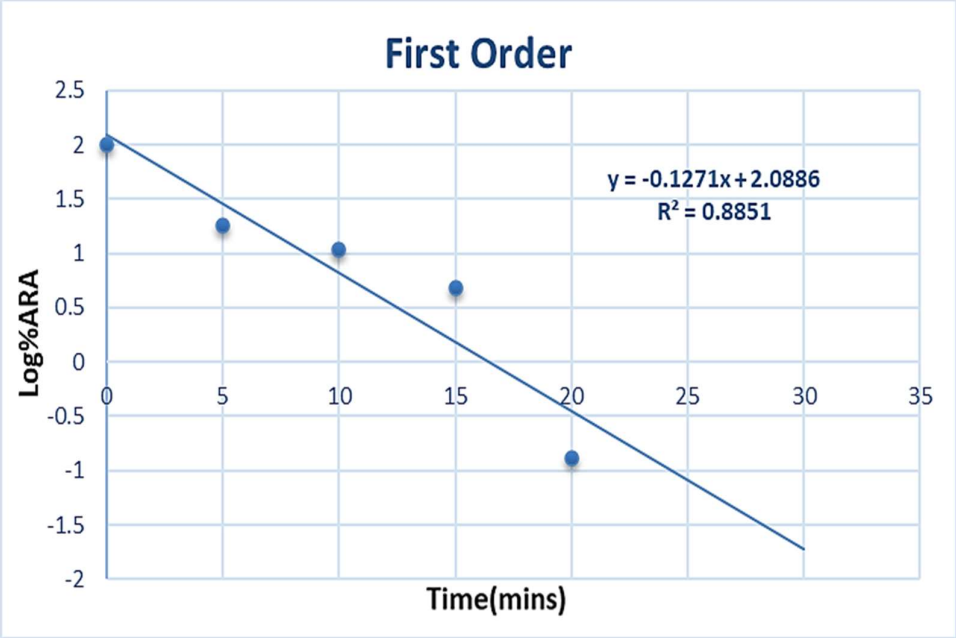

Fig 12: First order plot of (F6C6)

CONCLUSION

Xylitol and Mannitol was employed in the solvent evaporation process to create solid dispersions. Lamotrigine with SSG is being studied for its ability to dissolve (1:3). indicates improved medication release. Additionally, all of the created solid dispersions underwent evaluation, with the results detailed in the preceding information.

The following conclusions were drawn from the present investigations.

From the Solubility studies in various buffers, we can say that 0.1N HCL buffer has more solubility when compared to other buffer solutions for Lamotrigine.

Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug and optimized formulation (drug + excipients) which indicates there are no physical changes. All the formulations of Lamotrigine were prepared solvent evaporation method. All the prepared solid dispersions were evaluated for drug content. The invitro dissolution studies of Lamotrigine was performed.

From the optimized formulation of the solid dispersions(i.e., F6) weight equivalent of Lamotrigine was used along with the super disintegrants like Mannitol & PEG-4000.

Pre compression and Post compression evaluation studies were performed.

The better drug release with 9% PEG-4000 with 99.87% of drug release at the end of 20mins.

Drug release kinetics of the optimized formulation shows First order drug release.

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