FORMULATION AND IN VITRO EVALUATION OF LAMOTRIGINE ORAL THIN FILMS

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ABSTRACT

There is rapidly dissolving dosage forms have great important in the pharmaceutical industry due to their unique properties and advantage. The objectives of the present study is to design and evaluate fast dissolving films of lamotrigine using HPMC different grade with an aim to achieve rapid drug release thereby controlling the seizures in the shortest possible time. The films were prepared by the solvent casting method using different concentration of sodium starch glycolate (SSG) as a super disintegrate, croscarmellose sodium (CCS), hydroxypropyl methylcellulose (HPMC), carboxy methyl cellulose (CMC), Polyethylene glycol (PEG-400), vanilla as a flavoring agent and aspartame as sweetening agent. The prepared first dissolving film was evaluated both physically characterization thickness, weight variation, drug content, disintegration time, *in vitro* dissolution study, folding endurance and surface pH. The drug-excipient compatibility study was performed by using FT-IR. All the planned seven (L1-L7) formulations indicate attractive film parameter but optimized formulation (L4) was gave 98.7% of drug release at 15 min. The formulation L4 gave satisfactory pH (6.2 ± 0.2), drug content ($98.9 \pm 0.5\%$), the disintegration time of 3.0 ± 0.1 seconds and film thickness (0.17 ± 0.002 mm). The compatibility study was performed on optimized formulation L4 by using FT-IR which revealed that there was absence of any type of interaction between the drug and excipient. The 3 months stability study was carried as per ICH guidelines found that there is no significant change on optimized formulation L4.

Key word: Oral fast dissolving film (OFDF), Croscarmellose sodium (CCS), FT-IR, Solvent-Casting Method

INTRODUCTION:

Among all routes of drug administration, the oral route is one of the most favored routes. Oral course is the most favored course for the conveyance of the medications till date as it bears different focal points over the other course of medication organization, however oral medication conveyance frameworks still need a few headways to be made in light of their a few disadvantages identified with specific class of patients which incorporates geriatric, pediatric and dysphagia patients related with numerous restorative conditions as they experience issues in gulping or biting strong dose shapes [1,2]. There are many of the pharmaceutical industry focusing their research on rapid dissolving technology. Oral course

is the most favored course for the conveyance of the medications till date as it bears different focal points over the other course of medication organization. Oral fast dissolving film (OFDF) is one such novel approach to increase consumer acknowledgment by temperance of quick disintegration, self-organization without water or chewing. The film is a perfect intraoral quick dissolving drug conveyance framework, which fulfills the neglected needs of the market, is anything but difficult to deal with and oversee, keeps up a basic and advantageous bundling, lightens repulsive taste, and is clear to fabricate.

Buccal drug delivery recently becomes an important route of drug administration in which problems like high first-pass metabolism and drug degradation in the gastrointestinal environment can be avoided by administering the drug through buccal route. Thus, fast dissolving films allow the films to dissolve in the mouth, so the drug gets directly absorbed into the systemic circulation through the oral mucosa [3]. Innovative work in the oral medication conveyance section has prompted change of measurement frames from basic regular tablets or cases to altered discharge tablets or containers to oral disintegration tablet (ODT) to wafer to the current improvement of oral first dissolving films (OFDFs). Among the plenty of roads investigated for the fast medication discharging items, oral strip innovation is increasing much attention [6, 7]. (OFDT) was at that point well known among the general population in the mid 2000 year with the presentation and far reaching utilization of Listerine take strips, another dispatch in the mouthwash run. Innovation Catalysts figures the market for medicated items in oral thin film details to be esteemed at \$500 million of every 2007 and could reach \$2 billion in close future [7, 8, 12]. However just a couple of items comprising unpleasant particles have possessed the capacity to be popularized in light of the multifaceted nature related with the ODT. Oral fast dissolving film (OFDF) is one such novel approach to increase consumer acknowledgment by temperance of quick disintegration, self-organization without water or chewing. The film is a perfect intraoral quick dissolving drug conveyance framework, which fulfills the neglected needs of the market, is anything but difficult to deal with and oversee, keeps up a basic and advantageous bundling, lightens repulsive taste, and is clear to fabricate. The film is set on the best or the floor of the tongue. It is held at the site of use and quickly discharges the dynamic operator for neighborhood or potentially foundational absorption. The improvement of a quick dissolving film likewise gives a chance to a line augmentation in the commercial center, an extensive variety of medications (e.g., neuroleptics, cardiovascular medications, analgesics, antihistamines, antiasthmatic and drugs for erectile brokenness) can be considered possibility for this dose form [7,10-16].

Epilepsy is a neurological disorder which requires quick management of seizures in order to avoid the risk of permanent brain damage. More than 5.2 crores of people suffer with epilepsy of which only some 1.6 crores people avail proper therapy. Thus it is necessary to develop fast dissolving films for the anti-epileptic drug Lamotrigine is a new antiepileptic drug, which acts by blocking voltage-dependent sodium channel, and reducing the release of excitatory neurotransmitters, particularly glutamate and aspartate to bring brain back to orderliness.

MATERIAL AND METHODE:

Material:

Materials used in this study were obtained from different sources. Lamotrigine a gift sample from Chandra Lab, Hyderabad. Hydroxy propyl methyl cellulose (HPMC), carboxyl methyl cellulose (CMC) procured from Drug India Pvt.Ltd. Croscarmellose sodium (CCS), sodium starch glycolate (SSG), Polyethylene glycol (PEG-400), vanilla and aspartame were procured from S.D. Fine Chem. Ltd., Mumbai.

Preformulation study:

It is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients uses of which maximizes the chances in formulating an acceptable, safe, efficacious and stable product [16-17].

Pre-formulation studies were carried out to serve following purposes:

- i) To finalize specifications of active pharmaceutical ingredients (API)
- ii) To Study the compatibility between active and inactive ingredient
- iii) Characterization of reference product

It is divided in to two Subclasses.

1. API characterization,
2. Compatibility study

Characterization of Lomotrigrine:

These are preliminary characteristics of any substance which is useful in identification of specific material. Physical properties of API were studied like organoleptic properties, melting point and solubility etc. The result was tabulated in table 2,3& 4.

Drug Excipient Compatibility Studies:

Study was completed utilizing FT-IR spectrometer by the KBr pellet technique in the wavelength between range of 400 and 4000cm⁻¹ [23-24]. FT-IR Spectra of Lamotrigrine alone and optimize formulation (L4) were recoded. The range was considered for particular pinnacles of medication and polymer. The spectrum of FT-IR is shown in fig-2 &3.

Determination of $\lambda_{\max}$ of Lamotrigrine:

Accurately weighed 100 mg of Lamotrigrine and transferred into 100 ml of volumetric flask and dissolved in small quantity of methanol and diluted with pH 6.8 phosphate buffer up to the mark to give stock solution 1 mg/ml (100 μ g/ml). 1 ml was taken from stock solution in another volumetric flask and diluted up to 10 ml to give a stock solution 100 μ g/ml was examined between 200-400nm. The $\lambda_{\max}$ was observed to be 250nm and utilized as logical wavelength [25-26]. The spectrum as shown in fig-2

Preparation of Calibration curve of Lamotrigrine in pH 6.8 phosphate buffer:

From the above solution dilutions were made in phosphate buffer pH 6.8 in order to get 5, 10, 15, 20, 25 μ g/ml Absorbance of these dilutions were measured at $\lambda_{\max}$ 250nm using UV-Visible spectrophotometer and standard curve was plotted. The curve is shown in fig-1.

FORMULATION OF LAMOTRIGINE FAST DISSOLVING ORAL FILM:**Calculation of dosage for Lamotrigrine:**

Measurement of the glass Petri dish diameter = 4.8 cm

Zone area of the glass petri dish = $\pi r^2 = 18 \text{ cm}^2$

No. of 6 cm² (3x2cm) strip films display in entire plate = 18/6 = 3

Each film contains 35 mg of medication

3 no. of films contains Lamotrigrine = 3 x 35 = 105 mg

The measure of medication included each plate was around equivalent to 105 mg.

Preparation of Lamotrigrine by Solvent-Casting Method:

The Oral quick dissolving films were set up by dissolving strip framing operators and plasticizer in the refined water, at that point arrangement was constantly mixed up to 4 hours on attractive stirrer^[9,10,12,26] and kept for 1 hour to expel all the air bubbles ensnared. Then, in the different compartment remaining water solvent excipients i.e. sweetening specialist,

flavor and medication were disintegrated with steady blending for 45 min. At the point when the mixing was over both the arrangements were combined with blending for an additional 1 hour on attractive stirrer. At that point the arrangement was kept stationary for 1 hour to give the froths a chance to settle down [24-30]. The subsequent plan was cast on to a glass petri dish of surface zone 18 cm² dried for 24 hours at room temperature. The film was expelled from the plate painstakingly and watched for any defects. Film of territory 6 cm² (2 X 3) was cut and put away in a spread paper and secured with aluminum thwart and put away in a desiccator. Different formulation was prepared by incorporating different concentration of HPMC, CMC, SSG and CCS.

Table – 01: Formulation design

S.N	Ingredients	L1	L2	L3	L4	L5	L6	L7
1	Lamotrigine	35	35	35	35	35	35	35
2	SSG	0.5%	-	1%	-	0.5%	-	1%
3	CCS	-	0.5	-	1%	-	0.5%	-
4	HPMC	3%	4%	3%	3%	-	-	-
5	CMC	-	-	-	-	3%	4%	4%
6	PEG-400	0.1%	0.1	0.1%	0.1%	0.1%	0.1%	0.1%
7	Vanillin	0.2%	0.2	0.2%	0.2%	0.2%	0.2%	0.2%
8	Aspartame	0.2%	0.2	0.2%	0.2%	0.2%	0.2%	0.2%
Inference		Film not formed	Film formed	Film formed	Film formed	Film not formed	Film formed	Film formed

EVALUATION FILMS:**Weight variation of the film:**

2 x 3 cm² film was cut at five better places in the threw film. The heaviness of each filmstrip was taken and the weight variation [27,28] was figured and the outcomes are given in the table no.06

Thickness of the film:

The thickness of the fix was estimated utilizing advanced Vernier Callipers with a minimum check of 0.01 mm at various spots of the film. The thickness was estimated at three unique spots of the film [26-28] and normal was taken and SD was ascertained and given in the table no.06.

Folding endurance:

The collapsing perseverance is communicated as the number of folds required to break the strip. This gives a sign of weakness of the film. A little piece of 2x3 square cm was subjected to this test by collapsing the film at the same plane[26-29] over and again a few times until the point that an obvious break was watched and the outcomes are appeared in the table no-06.

pH: The pH was controlled by dissolving a film in 2 ml of distilled water and after that the pH of the acquired arrangement was estimated by pH paper[26-28].

Content Uniformity:

Drug content consistency of every one of the seven clumps was controlled by UV Spectrophotometric technique. For this, each strip at three better places identical to 35mg of medication was cut and broke down in 50ml of 6.8 pH phosphate buffer with consistent mixing. This arrangement was separated utilizing Whattmann filter paper, and the filtrate was made up to 100ml with 6.8pH phosphate buffer. This arrangement was investigated by UV Spectrophotometer and the absorbance [29-31] was recorded at 250nm. The outcomes were outlined in table no-06.

Disintegration time:

Test was performed utilizing deterioration test mechanical assembly. $2 \times 3 \text{ cm}^2$ film was put in the bin, brought and brought down it up. Time required by the film, when no hints of film [16, 17] stay over the dressing was noted. Test was performed in triplicate and the outcomes are accounted for in the table no-06.

Invitro Dissolution studies:

Drug release from OFDFs was studied by using USP Type1 dissolution test apparatus. OFDFs of desired formulation were placed in the vessels of dissolution apparatus. Samples were collected at time intervals of 2, 5, 10, 15, 20, 25, 30, 40 and 60 m, replenished with equal volume of the blank solution. The samples were filtered immediately and analyzed spectrophotometrically at 250nm [15-17]. Cumulative percentage Lamotrigine released was calculated and plotted against time. The outcomes are given in the table no.07.

Kinetic analysis of in vitro release data:

In order to determine the release mechanism that provides the best description to the pattern of drug release, the in vitro release data were fitted to zero order, first-order, Hixson Crowell, and Korsemeyer-Peppas model [35-38]. The data of regression coefficient of different kinetic models were summarized in table no-08.

Stability Studies:

The optimized batch F5 was packed in a butter paper covered with aluminum foil and was isothermally stressed to study the stability under accelerated temperature and relative humidity conditions carried out at 40°C/75% RH, 25°C/60% RH and 25°C/40% RH for a period of 3 months [41-43]. Test samples were withdrawn every month and were subjected to various tests including visual inspection of the film, disintegration time and cumulative percent of drug release. The results are given in Table-09.

RESULT AND DISCUSSION:**1. Preformulation Study:****A. Organoleptic Properties (Color, odor, taste and appearance)****Table- 02.** Results of identification tests of drug

S.NO	Parameter	Drug
1	Color	White to off white powder
2	Odor	Odorless
3	Taste	Tasteless
4	Appearance	Crystalline powder.

B. Melting point determination of Drug: Lamotrigine**Table 03:** Results of Melting point determination test of drug

DRUG NAME	Observed Melting Point
Lamotrigine	216-218 ⁰ c

C. Solubility

Results of the tests are illustrated in the table

Table no 04: Table showing the Solubility of Lamotrigine (API) in various solvents.

Solvents	Solubility
Water	Slightly soluble
pH6.8 Phosphate buffer	Soluble
Methanol	Soluble
Acetone	InSoluble

D. Standard Calibration Curve

In the pre-formulation study, it was found that the $\lambda_{\max}$ of Lamotrigine by spectrophotometric method in phosphate buffer pH 6.8 was found to be 250nm. The spectrum were shown in fig-01

*Fig no- 01 UV Spectrum for Lamotrigine at 250n***Table 05:** Calibration Curve of Lamotrigine in Phosphate Buffer pH 6.8

Concentration ($\mu\text{g/ml}$)	Absorbance
0	0
5	0.101
10	0.184
15	0.277
20	0.370
25	0.460

Fig2:Standard Graph of Lamotrigine in Phosphate Buffer pH 6.8

E. Drug polymer compatibility studies:

FTIR studies conducted on pure drug and the optimize formulation (L4) given in Figures 3 and 4, which showed that, there is no marked interaction between drug and excipients used.

Fig no-3FTIR spectra of Lamotrigine Pure Drug

Fig No-04 FTIR spectra of Lamotrigine optimize formulation (L4)

2. Characterization of Lamotrigine Fast Dissolving Oral Films

2.1 Weight Variation test

The weights of the films were observed to be in the range of 197mg to 206mg. The aftereffects of normal weight of all films were compressed.

2.2 Physical appearance and surface

The perception by visual examination of films and by feel or touch, recommends that the films are having smooth surface and they are sufficiently rich to see.

2.3 Thickness of films

The thicknesses of the films were in the scope of 0.16mm to 0.29mm. The consequences of normal thickness of all films were abridged in table no.6.

2.4 Folding endurance number:

Folding continuance of the films was observed to be in the scope of 98 to 108. The aftereffects of normal collapsing continuance of all films were outlined in table no.06.

2.5 In-vitro disintegration test:

The disintegration times were in the range of 3 min to 6 min. The results of average disintegration time of all films were summarized in table no-07

2.6 Drug content test:

Drug content is performed by taking three films in every detailing trial and the normal medication content was ascertained. The outcomes were observed to be in the scope of 94.4% to 98.9%. The consequences of normal medication substance of all films were condensed in table no.06.

Table 4: Evaluation of Lamotrigine Films (L1 to L7)

Formulation Code	Weight variation in mg	Thickness in mm	Folding endurance	Drug content in %	Disintegration time
L1	206	0.22	103	97.2	4 min
L2	203	0.29	108	95.8	6 min
L3	201	0.18	106	95.6	3 min
L4	198	0.17	98	98.9	3 min
L5	197	0.16	101	96.8	5 min
L6	205	0.21	104	94.4	2 min
L7	206	0.22	101	96	3 min

2.7 In-vitro dissolution test:

In-vitro drug release studies in 6.8 pH phosphate buffer show drug release from range 65.8% to 98.7% all film formulation within 15min. The plots of % aggregate Lamotrigine release versus time (min) were plotted and delineated as appeared in Fig.05. The formulation L4 indicated higher release rate of 98.7% uncovering that films made with convergences of

HPMC, 3% w/v and CCS 1% w/v. As higher dissolution rate helps in quicker beginning of activity, L4 was picked as the improved formulation.

Table 07: In-vitro drug release data of formulation L1 to L7

Time in min	L1	L2	L3	L4	L5	L6	L7
2	16.8	12.6	20.3	36.3	14.3	10.5	21.8
4	31.8	28.7	35.7	49.3	29.8	25.6	37.2
6	43.6	40.1	47.8	61.8	42.7	38.6	48.3
8	51.8	47.2	56.3	70.6	49.6	45.08	57.6
10	60.1	58.2	65.8	80.03	59.5	55.7	66.9
15	71.6	69.3	76.3	98.7	70.2	65.8	77.8

Fig no- 05 In-vitro drug release of formulations L1-L7

2.8. Data analysis (Curve fitting analysis):

For analyzing the release mechanism, the data obtained were fitted to various kinetic equations of Zero order, First order, Higuchi model and Korsmeyer - Peppas model. The regression coefficient is calculated. The data of regression coefficient of different kinetic models were summarized in table no.08.

Table 08:Regression data

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log %of drug release Vs T	%CDR Vs $\sqrt{T}$	LogC Vs Log T
Slope	6.00733945	-0.11398717	25.54912993	0.49912782
Intercept	18.13853211	2.156477161	-0.19652700	0.56741021
Correlation	0.950970768	-0.93512452	0.999691507	0.851049545
R²	0.904345402	0.873357878	0.99953831	0.7255285328

Fig no- 06 Zero order kinetics

Fig no-07First order kinetics

Fig no-08Higuchi order kinetics

Fig no-09 Korsmeyer-Peppas Model plot

3.0 Stability studies

The formulation of L4 was evaluated for stability studies which was stored at 40°C / 75% RH for 3 months and evaluated for their physical appearance, drug content and disintegration time and % drug release at the end of 1st and 3rd month. The results were summarized in table no.09

Table 9: Stability data of formulation L4

Formulation L5 stored at 40°C / 75% RH			
Time in month	Physical Appearance	Disintegration time(sec)	% Drug release
Initial	Transparent&acceptable	4	98.7
1 month	Transparent&acceptable	5	98.4
End of 3 rd month	Transparent&acceptable	4	98.1

SUMMARY AND CONCLUSION:

In current research work, an effort has been made to prepare Fast dissolving Lamotrigine oral film by solvent casting method. Pre formulation study involving FTIR study showed no interaction between drug and polymer. Fast dissolving films prepared in the study exhibited good film characteristic features as indicated by thickness measured, folding endurance, disintegration time, tensile strength and drug content. The prepared films containing 3% w/v of HPMC and 1% CCS film (formulation L4) showed 98.7% of drug was released by in 15 minutes which was desirable for fast absorption. As compared to that conventional dosage form, Fast dissolving Film has rapid onset of action. Data obtained from correlation coefficient and slope values revealed that drug release from formulation followed Higuchi model kinetic ($R^2=0.9995$), indicating diffusion as the release mechanism and “n” =0.49 indicate anomalous diffusion or non fickian diffusion. The optimized batch L4 was found to be stable for a period 3 months accelerated stability study at 40° C/75% RH. From the present examination it can be presumed that oral quick dissolving film definition can be a potential novel medication measurement frame for pediatric, geriatric and furthermore for all inclusive community for management of epilepsy.

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