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Research Article

Formulation development and *invitro* evaluation of lamotrigine fast dissolving tablets

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ABSTARCT

The present study was to formulate and evaluate oral fast dissolving Oral tablet containing Lamotrigine. Present study reveals that all the nine formulated tablet showed satisfactory tablet parameters. It can be concluded that, Oral fast dissolving tablet -containing Lamotrigine can be prepared by direct compression method. 10% CCS (FV) tablet exhibited required disintegration time and dissolution time. The drug release was about 98.7 % in 15min. The accelerated stability studies of the optimized F5 formulation indicates that the formulated oral fast dissolving tablet were unaffected after 3 months storage under accelerated conditions as there were no signs of visually distinguishable changes in appearance, disintegration time and cumulative percentage of drug release. From the present investigation it can be concluded that oral fast dissolving tablet formulation can be a potential novel drug dosage form for pediatric, geriatric and also for general population.

Keywords: Direct compression method, Lamotrigine, Disintegration time

INTRODUCTION

ORAL DISINTEGRATING TABLET

The most important drug delivery route is undoubtedly the oral route. It offers advantages of convenience of administration and potential manufacturing cost savings. Drugs that are administered orally, solid oral dosage forms in general and tablets in particular represent the preferred class of product. Today drug delivery companies are focusing on solid oral drug delivery systems that offer greater patient compliance and effective dosages[1]. Tablet is the most popular among all dosage forms existing today because of its convenience of self-administration, compactness and easy manufacturing. Many patients find it difficult to swallow tablets and hard gelatin capsules and do not take their medication as prescribed. In a survey conducted by Honda and Nakano, half of the patients experienced difficulty taking medication, such as tablet and capsule which results in a high incidence of non-compliance and ineffective therapy. The difficulty is experienced in particular by pediatric and geriatric patients, but it also applies to people who are ill in bed

and to those active working patients who are busy or traveling, especially those who have no access to water[2]. Oral disintegrating tablets offer an advantage for populations who have difficulty in swallowing. It has been reported that dysphagia (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients and patients with nausea, vomiting and motion sickness complications. Oral disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets and rapimelts. Recently, European Pharmacopoeia has used the term orodispersible tablet for tablets that disperses readily and within 3 min in mouth before swallowing.United States Food and Drug Administration (FDA) defined ODT as "A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." The disintegration time forODTs generally ranges from several seconds to about a minute[3].

METHODOLOGY MATERIALS

CHEMICALS

The following drug lamotrigine purchased from Chandra labs, Hyderabad and the following excipients like mannitol, MCC 101, croscarmelose sodium, crospovidone, sodium starch glycolate are purchased from S.D fine chemicals. And aerosol, aspartame, and magnesium stearate are ppurchased from Drug India Pvt. Ltd.

CHARACTERIZATION

ORGANOLEPTIC EVALUATION

Organoleptic characters like color, odor, and taste of drug were observed and recorded using descriptive terminology.

ANALYTICAL EVALUATION

UV ABSORPTION MAXIMA (Λ_{MAX}) OF DRUG SAMPLE

Stock II: One ml of the above solution was then further diluted to 100 ml with phosphate buffer to get a stock solution of 10µg/ml. UV scanning was done for 10 µg/ml drug solution from 200-400 nm using 6.8pH as a blank in schimadzu, UV 2450 spectrophotometer. The wavelength maximum was found to be at 270 nm.

PREPARATION OF STOCK SOLUTION

Stock I: 100mg of the drug was accurately weighed and transferred into the 100 ml volumetric flask. It was dissolved in sufficient quantity of water and volume was made up to the mark with 6.8pH phosphate buffer to get a 1000 µg/ml solution. This was the standard stock solution containing 1 mg/ml of model drug. (Stock I).

Stock 2: from above stock 1 solution 10ml was taken and make up with 6.8pH phosphate buffer to 100ml and this was 100ppm concentration solution.

PREPARATION OF THE CALIBRATION CURVE

From the stock II solution 0.2, 0.4, 0.6, 0.8, 1.0 and 1.2 ml were transferred to 10 ml volumetric flasks and were diluted with 6.8pH phosphate buffer up to the mark to obtain concentration of 2, 4, 6, 8, 10 and 12µg/ml respectively. Absorbance of each solution was measured at 270 nm. The Standard curve preparation was performed. The absorbances on x-axis were plotted against the concentrations on y-axis and r^2 value was obtained.

PRE-FORMULATION STUDIES

FT-IR STUDIES

The IR absorption spectra of the lamotrigine drug and with different superdisintegrants, natural gums and excipients were taken in the range of 4000-450 cm^{-1} using KBr disc method, 1-2 mg of the substance to be examined was triturated with 300-400 mg, specified quantity, of finely powered and dried potassium bromide .These quantities are usually sufficient to give a disc of 10-15mm diameter and pellet of suitable intensity by a hydraulic press. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks due presence superdisintegrants and excipients.

FORMULATION PLANNING

Oral disintegrating tablets containing lamotrigine were prepared with a total tablet weight of 200mg. By conducting the thorough literature survey, the excipients were selected and an attempt was made to produce oral disintegrating tablets which are having

ideal mouth feel and maintained the basic tablet properties.

GENERAL FORMULA

Different superdisintegrants croscarmellose sodium, crospovidone, Sodium starch glycollate in the concentration range of 6- 15%.. Microcrystalline cellulose (Avicel PH102) was selected as the filler or diluent, owing to its multiple functionalities as binder, disintegrant, compressibility and flowability. Out of the various grades available, the granular form - Avicel PH102 was selected for direct compression purpose, because it had been already reported to provide lower crushing strengths and shorter disintegration times. Mannitol was selected to produce a cooling and pleasant mouth feel, it was reported that mannitol above the concentration of 33% gives good mouthfeel, thus mannitol in all the batches was fixed at a concentration of 40-47%. Besides mannitol also possesses sweetening properties and reduces the gritty mouth feel effect due to microcrystalline cellulose. It also has good compressibility properties and solubility in water. To improve flow property of the blend magnesium stearate (1- 4%) and aerosil (1%) as glidant and lubricant were incorporated, magnesium stearate also decreases the hardness of tablets without affecting the disintegration time. Aspartame was used in the concentration of 2- 6% as the flavoring agent.

FORMULATION OF DIFFERENT BATCHES

The main aim of the present study was to formulate different batches using three various superdisintegrants and other ingredients in varying concentrations. So, different batches of formulations were planned accordingly. According to that F1, F2, F3 (with Crospovidone-3%, 5%, 7.5%), F4, F5, F6 (with Crosscaramellose-3%, 5%, 7.5%), F7, F8, F9 (with Sodium starch glycollate-3%, 5%, 7.5%). The slight bitter taste of the drug was masked using aspartame and mannitol as the flavoring & sweetening agent respectively.

Table 1: Formulations of Different Batches (F1-F9){ Total tablet weight 200mg}

Formulations Code									
Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Lamotrigine	25	25	25	25	25	25	25	25	25
Crospovidone	6	10	15	------	------	-------	------	------	-----
Croscarmellose sodium	------	------	------	6	10	15	------	------	-----
SSG	------	-----	----	-------	------	-----	6	10	15
MCC 101	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Aspartame	4	4	4	4	4	4	4	4	4
Mannitol	75	75	75	75	75	75	75	75	75

Magnesium stearate	3	3	3	3	3	3	3	3	3
Aerosil	2	2	2	2	2	2	2	2	2

METHOD OF FORMULATION

DIRECT COMPRESSION METHOD[13]

The model drug (lamotrigine) is thoroughly mixed with the superdisintegrants and then other exipients are added to the mixer and passed through the sieve (sieve no. 40). Collected the powder mixer, blended with magnesium stearate (pre sieved through sieve no. 60), the powder blend is subjected to drying for removal of moisture content and then subjected the blend for tablet compression by using Round and flat faced punches in CADMACH 16 punches tablet punching machine. Punches of 8 mm diameter were used for compression. Tablet of 200 mg was prepared by adjusting hardness and volume screw of compression machine properly**.**

Table 2: Summary of general dissolution conditions

Sl. No.	Parameter	Specifications
1.	Dissolution medium	$6.8P^H$
2.	Temperature	37 ± 0.5^oc
3.	Rotation speed	50 rpm
4.	USP Type II	Paddle
5.	Volume withdrawn	5 ml every 2 minutes
6.	λ_{max}	270

RESULTS AND DISCUSSION

CALIBRATION CURVE

Table3: Concentration and Absorbances

S.NO	Concentration	Absorbances
1	0	0
2	2	0.082
3	4	0.163
4	6	0.246
5	8	0.326
6	10	0.403

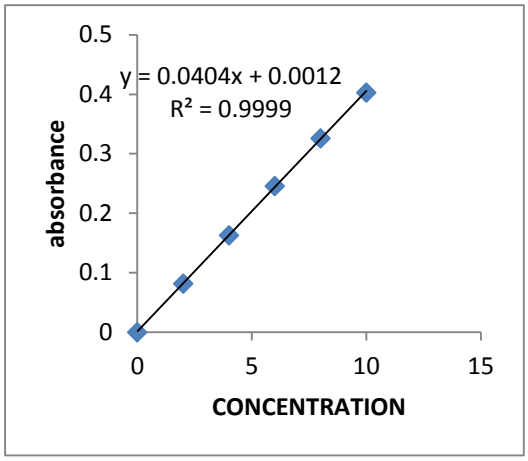

FIG:1 Calibration curve of Lamotrigine

PRE-FORMULATION STUDIES

The following preformulation studies were performed for Model drug

SOLUBILITY

Soluble in DMSO (12 mg/mL) at 40 °C, ethanol (12 mg/mL) at 40 °C, DMF (25 mg/mL), methanol, and dilute hydrochloric acid (slightly soluble). soluble in water.

MELTING POINT

The Melting point of obtained drug sample was found to be 216°C**.**

SPECTROSCOPIC STUDIES

FT-IR SPECTROSCOPY

The FT-IR spectrum of the pure drug was found to be similar to the standard spectrum of Lamotrigine. The spectrum of Lamotrigine showed the following functional groups at their frequencies mentioned in the table no 4

Table 4: Functional Groups And Frequencies

S.no	Functional group	Frequency range	Pure drug	Opt. Formulation
1	C – N	1335 – 1250	1310	1300.09
2	C = C	3100 – 3000	3065.07	3015.21
3	N- H	1650 – 1500	1527.06	1647.60

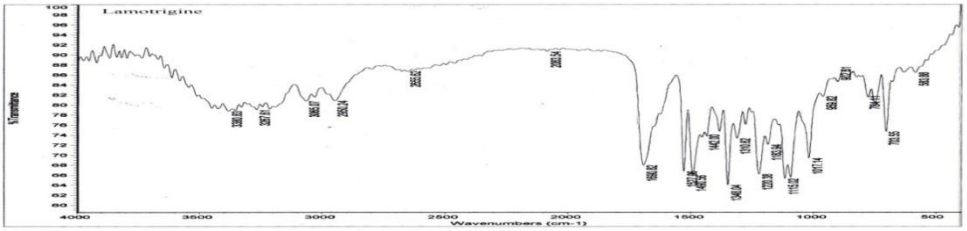

Fig 2. FT-IR Spectrum of Pure Drug (Lamotrigine)

COMPATIBILITY STUDIES

From the FT-IR Spectra of pure drug and the combination spectra of drug with the polymers, it was observed that all the characteristic peaks of drug are present in the combination spectra as well thus indicating the compatibility of the drug with the polymers used. The FT-IR Spectra of optimized formulation **(F5)** are shown in fig 2,3& table no 6.

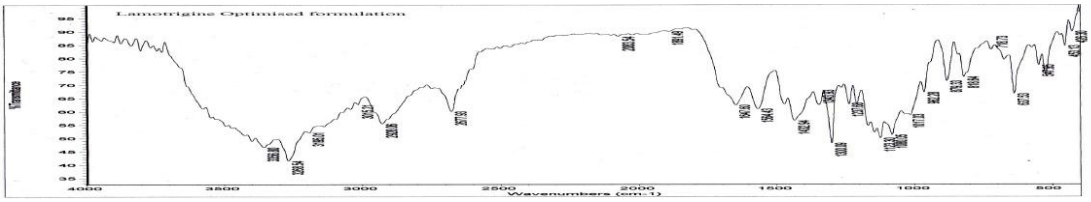

Fig 3. FT-IR Spectrum of Optimized Formulation F5

PRE-COMPRESSION PARAMETERS

The flow properties of the formulations were found to be in limit and the optimisied formula was in limit and has a fair flowing property.this had no effect during compression of tablets.table 5

Formulation	Blend Property					
	B.D(gm/ml)	T.D(gm/ml)	C.I (%)	H.R	Angle of repose	Property
F1	0.721	0.87	17.126	1.206	27.280	Fair
F2	0.461	0.608	24.177	1.32	24.210	Passable
F3	0.41	0.483	15.113	1.178	26.160	Fair
F4	0.710	0.873	19.714	1.251	29.320	Fair
F5	0.453	0.583	22.299	1.288	22.430	Passable
F6	0.500	0.600	23.22	1.295	23.460	Passable
F7	0.462	0.607	24.177	1.32	24.211	Passable
F8	0.722	0.868	17.129	1.206	27.290	Fair
F9	0.460	0.609	24.176	1.32	24.213	Passable

INVITRO DISINTEGRATION TEST

The disintegration times of the prepared Tablets were in the range of 3 min to 6 mins. The results of Average disintegration time of all Tablets were summarized in table no 6.

Table 6 for evaluation parameters of Lamotrigine

Code	WeightVariation(mg)	Thickness in mm	Hardness	Drugcontent in %	Disintegration time
F_1	199	2.23	2.5	96.8	2mins
F_2	206	2.22	2.8	97.2	4mins
F_3	203	2.29	2.6	95.8	6mins
F_4	201	2.18	2.9	95.6	3mins
F_5	198	2.17	2.9	98.9	3secs
F_6	201	2.19	2.8	97.2	1mins
F_7	197	2.16	2.7	96.8	5mins
F_8	205	2.21	2.3	94.4	2mins

F_9	206	2.22	2.6	96	1.3mins

INVITRO DISSOLUTION STUDIES

Lamotrigine FDOT dissolution study was conducted in 6.8pH phosphate buffer solution as this was similar to the pH of simulated salivary fluid. A modified dissolution methodology was followed to simulate the conditions of the oral cavity. The dissolution volume consists of 300ml of 6.8pH phosphate buffer solution at 37±0.5˚C, which was rotated at 50rpm. Lamotrigine FDOT from each formulation was carried out in 6.8 pH phosphate buffer solution for 20min. The data of dissolution studies were summarized in table no.9 . The dissolution study was conducted for 15 min. The drug release was found to be in the range of 59.6% to 99.2% and the % drug release was maximum. The plots of % cumulative drug release versus time (min) were plotted and depicted as shown in Fig.22. The formulation F5 showed higher drug release of 98.7% was the optimized formulation as it shows a higher drug release in the dissolution study. As higher dissolution rate aids in faster onset of action, F5 was chosen as the optimized formulation.F6 formulation has shown drug release similar to that of the F5 formulation but due less concentration of croscarmellose sodium used makes the F5 formulation the best.

Table no.7 . Invitro drug release data of formulation F1 to F9

Time in min	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	12.1	16.8	12.6	20.3	36.6	30.9	14.3	10.5	21.8
4	19.8	31.8	28.7	35.7	49.3	51.2	29.8	25.6	37.2
6	29.5	43.6	40.1	47.8	61.8	66.2	42.7	38.6	48.3
8	36.4	51.8	47.2	56.3	70.6	72.1	49.6	45.8	57.6
10	49.5	60.1	58.2	65.8	80.3	86.2	59.5	55.7	66.9
15	59.6	71.6	69.3	76.3	98.7	99.2	70.2	65.8	77.8

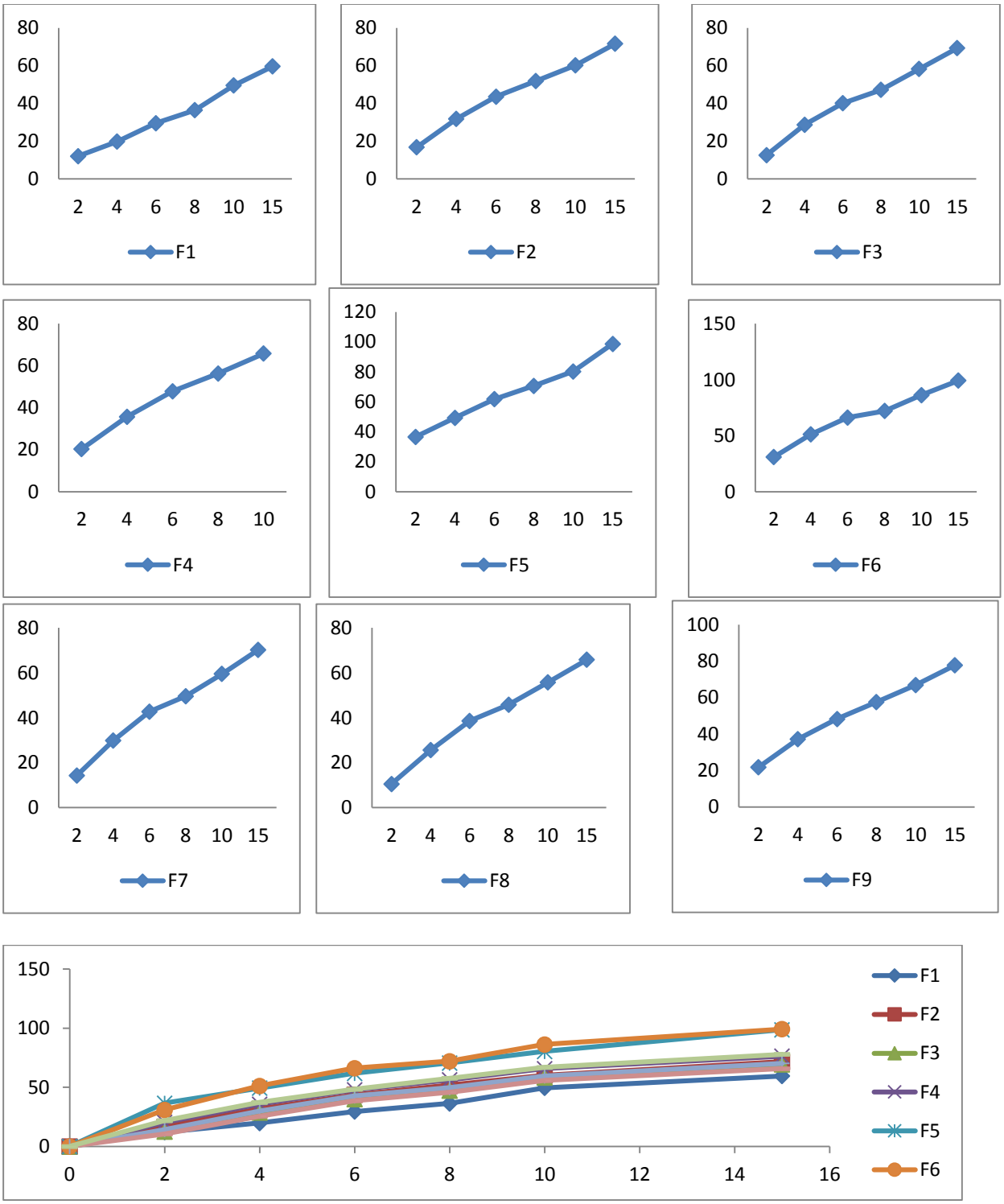

Fig.4. Invitro drug release data of formulation

DATA ANALYSIS (CURVE FITTING ANALYSIS)

For analyzing the mechanism of the drug release kinetics of the dosage form, 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.8.

REGRESSION DATA

Table 8

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	6.00733945	-0.11398717	25.34912993	1.433335473
Intercept	18.13853211	2.156477161	-0.19652700	0.56741021
Correlation	0.950970768	-0.93512452	0.999691507	0.851049545
R 2	0.904345402	0.874457878	0.99938311	0.724285328

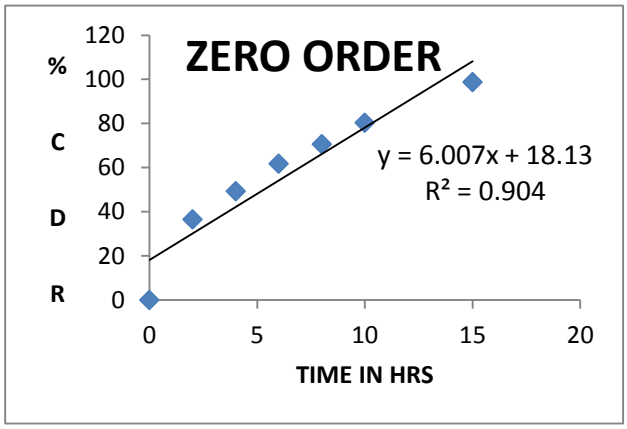

Fig 5:graph for zero order

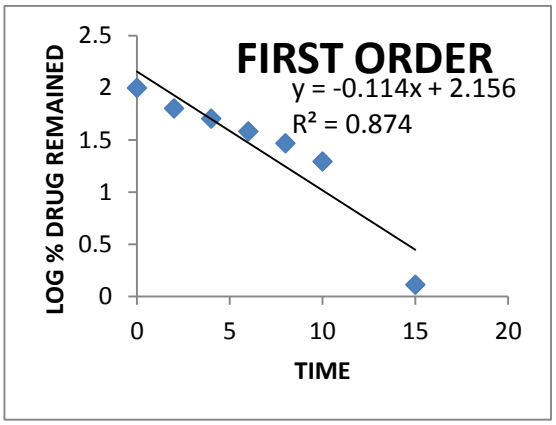

Fig 6:graph for first order

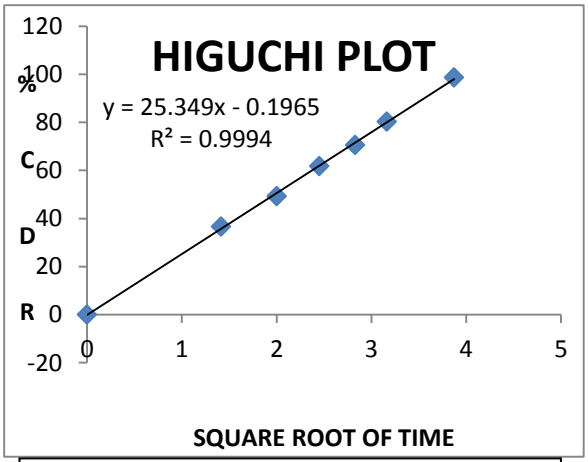

Fig 7:graph for higuchi plot

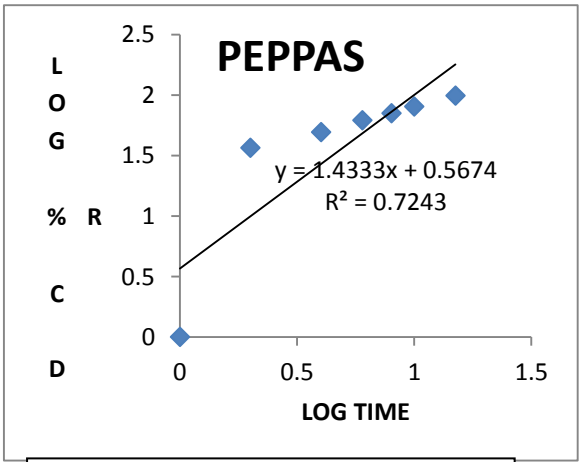

fig 8:graph for peppas

STABILITY STUDIES

The formulation of F5 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 invitro disintegration time and % drug release at the end of 1st and 3rd month. The results were summarized in table no.9

Table no.9 Stability data of formulation F5

Time in months	Formulation F5 stored at 40˚C / 75% RH		
	Physical appearance	**Disintegration time in sec**	**% Drug release**
Initial	Acceptable	4 sec	98.6
After 1 month	Acceptable	5sec	98.4
End of 3rd month	Acceptable	4 sec	98.1

DISCUSSION

The main objective of the study was to formulate and evaluate oral fast dissolving Oral tablet containing Lamotrigine. Compatibility of Lamotrigine with excipients was confirmed by FT-IR studies. Nine formulations were evaluated for weight variation and thickness showed satisfactory results. Disintegration time of the ODTs were decreased with increase in the concentration of the Super disintegrants, as less fluid is required to wet the tablet in the mouth. The presence of disintegrant showed a considerable effect on the disintegration time of the tablet. Content uniformity study showed that the drug is uniformly distributed in the tablet.

SUMMARY

The following parameters were summarized as

Disintegration time; the disintegration times of the prepared tablets were in the range of 3min to 6 min. in that F5 formulation disintegrates in 3secs (approximately)

Dissolution time; as higher dissolution rate aids in faster onset of action, F5 has chosen as the optimized formulation. F6 formulation as shown drug release similar to that of the F5 formulation .but due to less concentration of croscar mellose sodium used makes the F5 formulation the best.

CONCLUSION

Present study reveals that all the nine formulated tablet showed satisfactory tablet parameters. It can be concluded that, Oral fast dissolving tablet -containing Lamotrigine can be prepared by direct compression method. 10% CCS (FV) tablet exhibited required disintegration time and dissolution time. The drug release was about 98.7 % in 15min. (approximately). The accelerated stability studies of the optimized F5 formulation indicates that the formulated oral fast dissolving tablet were unaffected after 3 months storage under accelerated conditions as there were no signs of visually distinguishable changes in appearance, disintegration time and cumulative percentage of drug release. From the present investigation it can be concluded that oral fast dissolving tablet formulation can be a potential novel drug dosage form for pediatric, geriatric and also for general population

REFERENCES

[1]. Pranzatelli M R. Innovations in drug delivery to the central nervous system. Drugs Today. 1999; 35(6):435.

[2]. Ivares P. Formulation and evaluation of zolmitriptan fast disintegrated tablets prepared by direct compression. Norbotten:Lulea University of Technology; 2009.

[3]. Rapoport AM, Ramadan AM, Adelman. Optimizing the dose of zolmitriptan for the acute treatment of migraine. Neurology.1997 Nov; 49(5):1210-8.

[4]. Danavena R , Bhoomaiah B, Phani.R.S.CH, K Balamurali krishna. Validated RP – HPLC method for the estimation of zolmitriptan in formulation. Pharmacophore.2011; 2(2):150-5.
[5]. Soloman GD, Cady RK, Klapper JA, Earl NL, Saper JR, Ramadan NM. Clinical efficacy and tolerability of 2.5 mg zolmitriptan for the acute treatment of migraine. Neurology. 1997 Nov; 49(5):1219-56.
[6]. Visser WH, Klein KB, Cox RC, jones D. Ferrari MD. 311C90 a new central and peripherally acting 5-HT1D receptor agonist in the acute oral treatment of migraine: a double-blind, placebo-controlled, dose-range finding study. Neurology. 1996 Feb; 46(2):522-6.
[7]. Kumaresan C. Orally Disintegrating Tablet-Rapid Disintegration, Sweet Taste, and target Release Profile.2008 Sep; 6(5):435-8.
[8]. Biradar SS, Bhagavati ST. and Kuppasad IJ. Fast Dissolving Drug Delivery Systems. The Internet journal of pharmacology.2006; 4(2):567-9.
[9]. Kumar R, Patil MB, Patil SR, Paschapur MS. Development and Characterization of Melt-In-Mouth Tablets of Haloperidol By Sublimation Technique. International journal of pharmacy and Pharmaceutical sciences. 2009 July-Sep; 1(1):65-73.
[10]. Radke RS, Jadhav JK, Chajeed MR. Formulation and Evaluation of Orodispersible Tablets Of Baclofan. International Journal of ChemTech Research. 2009 July-Sept; l(3): 517-21