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Formulation and Evaluation of Bi-Layeres Tablet of Lamictal Lamotrigine

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ABSTRACT:
Lamictal (Lamotrigine) is an anti-epileptic medication used in treatment of epilepsy and bi-polar disorder. It works by stabilizing electrical activity in the brain and preventing excessive firing of nerve cells. The common side effects are dizziness, headache, nausea and rash. Overall Lamictal represents a valuable treatment option for individuals with epilepsy and bi-polar disorder and improving quality of life. 1

KEY WORDS: Epilepsy; gastro retentive drug delivery system; hydroxy propyl methyl cellulose. 2

I. INTRODUCTION:

Epilepsy (sometimes referred to as a seizure disorder) is a common chronic neurological condition that is characterized by recurrent unprovoked epileptic seizures. Epileptic seizures result from abnormal, excessive or hyper synchronous neuronal activity in the brain. About 50 million people world-wide have epilepsy and nearly 80% of epilepsy occurs in developing countries. Epilepsy is usually controlled, but not cured, with medication. Lamotrigine (LM) is an antiepileptic agent used as a monotherapy and as an adjuvant with other antiepileptic agents for the treatment of partial seizures, primary and secondary generalized tonic — clonic seizures. LM is a biopharmaceutical classification system (BCS) class II drug with pH dependent solubility (solubility in water is 0.17 mg/mL at 25°C while that in 0.1 M HCl 4.1 mg/mL at 25°C). LM is an amine containing compound with a good solubility in the acidic or the gastric media and its solubility decreases with increasing ph. Gastric retention of such a drug facilitates better absorption on account of its higher solubility at stomach's acidic ph. It is rapidly and completely absorbed after oral administration with negligible first pass metabolism and requires multiple dosing (2-3 times daily) for maintaining the therapeutic effect throughout the day. 3

Existing formulations of LM provide immediate release with t_m ranging from 1.4 h to 4.8 h and result into a release profile exhibiting cyclic peaks and troughs. LM requires an extended-release delivery system with differential control mechanisms in the gastric and intestinal regions to overcome its pH-dependent solubility. Glaxo SmithKline's (GSK) manufactures Lamictal extended release (XR) tablets using conventional pharmaceutical excipients typical of those used for extended-release tablets. Lamictal XR extended-release tablets use the differential control release (DIFFCORE) technology in combination with an enteric coat and a polymer system that swells and erodes to control the release rate of LM. Lamictal XR tablets are drilled on two sides of the tablets and this modified release system is designed to deliver drug for 12-15 h.

Side-effects of the drug such as drug rash eosinophilia and systemic symptoms syndrome, Stevens-Johnson syndrome and toxic epidermal necrolysis caused by unregulated plasma concentrations of LM and the method of manufacturing using DIFFCORE technology is highly laborious and expensive. In order to overcome the limitations of the available formulations, it was proposed to develop a less laborious, economic and an industrially applicable method for the delivery of LM with improved solubility and plasma concentrations within the therapeutic window over an extended period of

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time. Therefore, we consider gastro retentive mucoadhesive formulation of LM as one of the most attractive routes for the oral delivery of LM. Gastro retentive drug delivery system is the technique in which the formulation is retained in the stomach for longer duration of time and hence the bioavailability of the drugs is improved preferentially absorbed from proximal gastro intestinal tract. Gastro retentive dosage forms are of four main classes: (i) Floating systems, (ii) expandable systems, (iii) bio adhesive systems and (iv) high density systems. Floating systems are of two types: Effervescent systems, depending on the generation of carbon dioxide gas upon contact with gastric fluids and non-effervescent systems. The latter systems can be further divided into four sub-types, including hydro dynamically balanced systems, micro porous compartment systems. Alginate beads and hollow microspheres/ micro balloons.

Floating drug delivery is of particular interest for drugs which:

- act locally in the stomach;
- are primarily absorbed in the stomach;
- are poorly soluble at an alkaline pH;

Have a narrow window of absorption and sare unstable in the intestinal or colonic environment. In the present work bilayered effervescent floating tablets of LM were developed using excipients such as hydroxy propyl methyl cellulose (HPMC) grades (K100M, K15M, K4M, HPMC K100, HPMC E50 LV), hydroxypropyl cellulose (HPC)-M, Sodium bicarbonate, Ethyl cellulose E1415, polyvinyl pyrrolidine (PVP) K30, Xanthan gum, Eudragit RS100. Sodium bicarbonate on contact with gastric fluid releases CO_2, which makes the tablet buoyant and improve the residence time at gastric pH. 4

METHODS AND MATERIALS:

Lamotrigine was obtained as a gift sample from Glenmark, Mumbai, soya lecithin was purchased from Himedia Lab. Mumbai, DMSO, and methanol were procured from Merck chemicals, Mumbai. Ethanol was procured from Changshu Hong sheng Fine Chemical Co. Ltd Jiangsu Province. Chloroform was purchased from Loba Chemise Mumbai, croscarmellose sodium from Akhil Healthcare Mumbai and cross povidone was obtained from Amnem Mumbai, sodium starch glycolate was purchased from Sigma Aldrich, Mumbai. All the chemicals used in experiments were of analytical grade. 5

PREPARATION:

All the ingredients were weighed accurately and passed through 40#, sieve blended in a poly bag except magnesium stearate for 10 min. The obtain mixture was wet massed using water (q. s) for granulation and was passed through 20#sieve in order to form granules. These granules were dried and were passed through 30# sieve. These dried granules were lubricated with magnesium stearate, which was previously through 60# sieve. The lubricated granules were punched into tablets using rotary punching machine (RIMEK) 6

Risk of bias

The Cochrane risk of bias assessment resulted in an AHRQ (Agency for Healthcare Research and Quality) rating of Good for three studies, Fair for three studies and Poor for seven studies. Judgements for individual items of the risk of bias assessment for each study are available in the supplementary material. Most studies were judged as having a low risk of bias for randomisation, blinding and selective reporting. However, more than half of the studies were considered to present an unclear or high risk of bias for incomplete outcome data, frequently due to relatively high dropout rates. Other potential sources of bias were identified for all studies, but in most cases, it was considered that there was insufficient evidence to assess the degree to which these problems might introduce additional bias, and as a result, the majority of studies were judged as having unclear risk for this item.

Experimental Design:

Experimental design utilised in present investigation for the optimisation of polymer concentration such as, concentration of HEMC K4M was taken as X1 and concentration of HPMC K100M was taken as X_2. Experimental design was given in the table 1. Three levels were selected and coded as -1= 7.5 % ,0=12.5%, + 1 =17.5%. Formulate for all the experimental batches were given in the table2.

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Table: 1 EXPERIMENTAL DESIGN LAYOUT

Formulation Code	X_1	X_2
F1	1	1
F2	1	0
F3	1	-1
F4	0	1
F5	0	0
F6	0	-1
F7	-1	1
F8	-1	0
F9	-1	-1

Table: 2 FORMULATE FOR THE PREPARATION OF LAMOTRIGINE SUSTAINED RELAESE TABLETS AS PER EXPERIMENTAL DESIGN

Name of the ingredients	Quantity of ingredients per each table(mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lamotrigine	200	200	200	200	200	200	200	200	200
Mannitol	58	78	98	78	98	118	98	118	138
HPMC K4M	70	70	70	50	50	50	30	30	30
HPMC K100M	70	50	30	70	50	30	70	50	30
Purified water	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Total weight	400	400	400	400	400	400	400	400	400

Evaluation of Lamotrigine

Weight variation

A total of 20 tablets were selected randomly from each batch and weighed using analytical balance. The average weight and standard deviation were calculated and not more than two tablets should deviate from the average weight by more than 7.5%.

Hardness: Tablet hardness was measured using a Monsanto hardness tester. The crushing strength of 10 tablets with known weight and thickness of each was recorded in kg/cm2 and their average hardness with standard deviation was calculated.

Friability:

A total of 20 tablets were selected from each batch and weighed. Each group of tablets was rotated at 25 rpm for 4 min (100 rotations) using Roche fabricator. The tablets were then dusted and re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original tablets. Conventional compressed tablets that lose < 0.5-1% of their weight were considered acceptable.

Diametrical fracture: It is a qualitative attribute concerned with the breaking of the tablet diametrically as opposed to de-laminating or capping and was tested by simple visual inspection.

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Thickness:

The thickness in millimetres (mm) was measured individually for 10 pre-weighed tablets using screw gauge and their average thickness with standard deviation were calculated.

In vitro buoyancy studies:

In vitro buoyancy was determined by observing floating lag time (FLT) and floating time. The tablets were placed in a beaker containing 100 ml of 0.1N HCl. The time taken for the dosage form to emerge to the surface of the medium is called FLT or buoyancy lag time and the total duration of time up to which the dosage form remain buoyant is called total floating time (TFT).

In vitro release studies:

The in vitro release studies of LM bilayered and single layered tablets were conducted using USP apparatus – II, fitted with paddle (50 rpm) at 37 ± 0.5°C using 900 ml of 0.1 NHCL as dissolution medium. Samples of 5 ml were withdrawn at 1, 2, 3, 4 and 5 up to 18 h at regular 1 h intervals and replaced with same volume of fresh medium. The samples were analysed by ultraviolet spectrophotometry at 244 nm and thecumulative percentage release was calculated using the standard calibration curve.

Drug release kinetics:

Drug release kinetics was studied by plotting zero order, first order, Higuchi and Korsmeyer-Peppas equations. Regression coefficients(r2) were calculated for all the formulations and the release component "n" was calculated from Korsmeyer-Peppas equation. Based on the "n" value release mechanism was characterized.

Calculation of similarity and difference factors:

The dissolution results obtained from the single layered formulation was set as reference (Rj) and the results of the optimized bilayered formulation (Tj) was compared using difference factor (f_1) and similarity factor (f_2)

The similarity factor was calculated with the formula $f_2 = 50 \times \log$

The difference factor was calculated with the formula:

Rj – Tj|Rjft = × 100nj = 1nj = 1

Accelerated stability studies for the optimized formulations:

Accelerated stability studies were conducted for the optimized formulations as per ICH guidelines. The studies were carried out at 40°C/75% RH for 3 months. The samples were withdrawn for every 1 month and evaluated for physical properties such as appearance, hardness, floating property, dissolution and assay. 6

Mechanism of action:

The mechanism of action for lamotrigine is not entirely understood. It is a triazine, and research has shown that lamotrigine selectively binds and inhibits voltage-gated sodium channels, stabilizing presynaptic neuronal membranes and inhibiting presynaptic glutamate and aspartate release. Researchers have not demonstrated that lamotrigine has significant effects on other neurotransmitters such as serotonin, norepinephrine, or dopamine. There is a theory that lamotrigine may interact with voltage-activated calcium-gated channels, contributing to its broad range of activity. In vitro studies have also shown that lamotrigine inhibited dihydrofolate reductase, potentially contributing to concerns for its teratogenicity. Lamotrigine follows first-order kinetics with a half-life of 29 hours. 7

II. RESULT AND DISCUSSION:

Lamotrigine oral Disintegration Tablet Formulations were prepared by direct compression methods using various proportions of super disintegrants combination as per the formulae. All formulations containing 25mg of Lamotrigine (as Lamotrigine SD with PEG as 1:1 ratio) prepare and evaluated for various pharmacopoeias limits such as, drug contents, mean hardness, friability, means thickness, weight variation as per official methods. The thickness values were found in the range from 3.15±0.02mm to 3.23±0. 02mm.Uniformity in the values indicates that formulations were compressed without sticking to the dies and punches. hardness was maintained to be within 3.85±0.21Kgcm^2 to 4.1± 0.3kg/cm2. The hardness of all batches was almost uniform and possess good mechanical strength. The study results for friability were found well within the approved range (<0.66%) in all formulation. Results revealed that the tablets possess good mechanical strength.

All the tablets passed weight variation test as the %weight variation within the pharmacopoeia's limits of ±5%. Average weight for all formulations was found to be in the range of 198.17±0.55-200.84±0.76mg. This is due to good flow property and compressibility of all the formulations.

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From the results wetting time and disintegration time, it reveals that as the concentration of super disintegrants increases the wetting time decreases (concentration of super disintegrants inversely proportional to wetting time.) Wetting time for all the formulations varied from 23.11±2.3 to 30.5± 1.81 sec. The disintegration time of tablets was in the range of 22.5±1.7-35.5±1.34sec.

Result for all post compression parameters were tabulated and plots for wetting time and disintegration were presented. The cumulative percentage drug released by each tablet in the in vitro release studies were based on the means content of the drug.

Cumulative % Drug release for F_1-F_9at 60min was found to be in the range of 99.21±0.66-99.84±0.01%. Dissolution profiles of lamotrigine oral disintegrating formulations were subjected to goodness of fit test by linear regression analysis according to kinetic modelling to as certain the drug release mechanism. the statistical parameters for kinetics models were determined. The values of r for formulations regarding Higuchi's kinetics within a range of 0.988-0.997, Kinetic data also treated for Peppas equation, the slope (n) values range from 0.492-0.643 that shows non-Fickian diffusion mechanism. Formulation F4 containing 40mg of crospovidone,35mg of sodium starch glycolate exerted promising dissolution parameter (Wetting time =24.5±1.8sec, Disintegrating time=29±1.54sec, t_{10}=0.926min, $t_{50\%}$6.091min, $t_{90\%}$20.240min). Results for kinetics parameters. The final best formulation F4 is compared with marketed product (LAMICTAL-25) tablets and comparative dissolution. Which shows similarity (f_2=73.17, f_1=3.65) ±

Table post-compression parameters

Formulation code	hard (kg/cm2)	Thickness (mm)	Friability (%)	Avgwt (mg)	Drug Content (%)	Wetting time (sec)	Disintegration (sec)
F1	4.05± 0.25	3.18± 0.02	0.54± 0.6	199.23± 0.45	98.3± 1.16	23.11±2.30	27.5± 1.76
F2	3.9± 0.2	3.15± 0.02	0.61± 0.38	199.84± 0.95	98.8± 2.04	24.5±2.26	29± 2.52
F3	4.05± 0.25	3.19± 0.023	0.65± 0.28	198.17± 0.55	98.04± 1.64	26.5±2.02	31.5± 2.03
F4	4.09± 0.265	3.19± 0.013	0.62± 0.19	200.05± 1.1	9.74± 1.31	24.5±1.8	29± 1.54
F5	3.85± 0.215	3.16± 0.013	0.54± 0.28	200.12± 0.54	99.24± 2.18	26±1.76	30.5± 2.3
F6	4± 0.265	3.2± 0.016	0.63± 0.07	199.17± 0.89	98.48± 1.79	28±1.53	33± 1.81
F7	4.1± 0.3	3.22± 0.015	0.62± 0.4	200.84± 0.76	99.2± 1.6	27±2.08	31.5± 1.1
F8	3.95± 0.25	3.19± 0.015	0.56± 0.4	200.83± 0.15	99.7± 2.48	28.5±2.04	33± 1.84
F9	4.1±0.3	3.23±0.018	0.61±0.39	200.26±0.44	98.94±2.08	30.5±1.81	35.5± 1.34

Statistical parameters

SI. NO	Formulation Code	Kinetic parameters											
		Zero order			First order			Higuchi			Korsmeyer peppas		
		a	b	r	a	b	r	a	b	r	a	b	r
1	F1	19.656	1.569	0.941	2.269	0.04	0.936	0.669	13.499	0.996	1.132	0.502	0.992

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2	F2	18.699	1.575	0.945	2.258	0.038	0.931	0.079	13.495	0.996	1.092	0.525	0.993
3	F3	15.612	1.574	0.962	2.212	0.032	0.929	2.046	13.258	0.997	1.009	0.564	0.996
4	F4	18.783	1.634	0.938	2.341	0.049	0.966	0.726	14.006	0.989	1.059	0.554	0.982
5	F5	17.894	1.637	0.941	2.217	0.04	0.977	1.403	13.978	0.988	1.017	0.577	0.982
6	F6	14.757	1.638	0.959	2.225	0.035	0.969	3.422	13.76	0.991	0.928	0.621	0.989
7	F7	15.3	1.604	0.963	2.251	0.035	0.944	2.486	13.472	0.995	1.004	0.57	0.994
8	F8	14.334	1.612	0.967	2.242	0.034	0.943	3.256	13.48	0.995	0.957	0.597	0.996
9	F9	11.223	1.612	0.98	2.238	0.031	0.922	5.242	13.247	0.991	0.863	0.643	0.995
10	Lamictal-25	21.116	1.57	0.925	2.415	0.051	0.879	1.504	13.635	0.988	1.156	0.492	0.975

Dissolution / kinetic parameters

Formulation

Code
Hardness (kg/cm2)
Thickness (mm)
Friability (%)
Avg wt (mg)
Drug Content (%)
Wetting time (sec)
Disintegration time (sec)

1 F1 4.05±0.25 3.18±0.02 0.54±0.6 199.23±0.45 98.3±1.16 23.11±2.30 27.5±1.76
2 F2 3.9±0.2 3.15±0.02 0.61±0.38 199.84±0.95 98.8±2.04 24.5±2.26 29±2.52
3 F3 4.05±0.25 3.19±0.023 0.65±0.28 198.17±0.55 98.04±1.64 26.5±2.02 31.5±2.03
4 F4 4.09±0.265 3.19±0.013 0.62±0.19 200.05±1.1 99.74±1.31 24.5±1.8 29±1.54
5 F5 3.85±0.215 3.16±0.013 0.54±0.28 200.12±0.54 99.24±2.18 26±1.76 30.5±2.3
6 F6 4±0.265 3.2±0.016 0.63±0.07 199.17±0.89 98.48±1.79 28±1.53 33±1.81
7 F7 4.1±0.3 3.22±0.015 0.62±0.4 200.84±0.76 99.2±1.6 27±2.08 31.5±1.1
8 F8 3.95±0.25 3.19±0.015 0.56±0.4 200.83±0.15 99.7±2.48 28.5±2.04 33±1.84
9 F9 4.1±0.3 3.23±0.018 0.61±0.39 200.26±0.44 98.94±2.08 30.5±1.81 35.5

SI.NO	Formulation code	Kinetic parameters		
		t1/2(min)	t10%(min)	t90%(min)
1	F1	7.547	1.147	25.08
2	F2	7.873	1.197	26.162
3	F3	9.364	1.423	31.117
4	F4	6.091	0.926	20.24
5	F5	7.588	1.153	25.217
6	F6	8.664	1.317	28.79
7	F7	8.484	1.29	28.192

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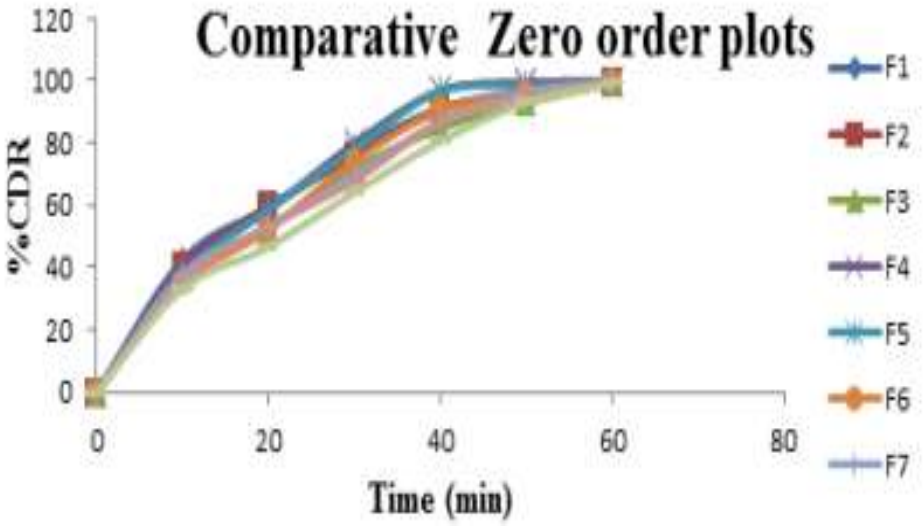
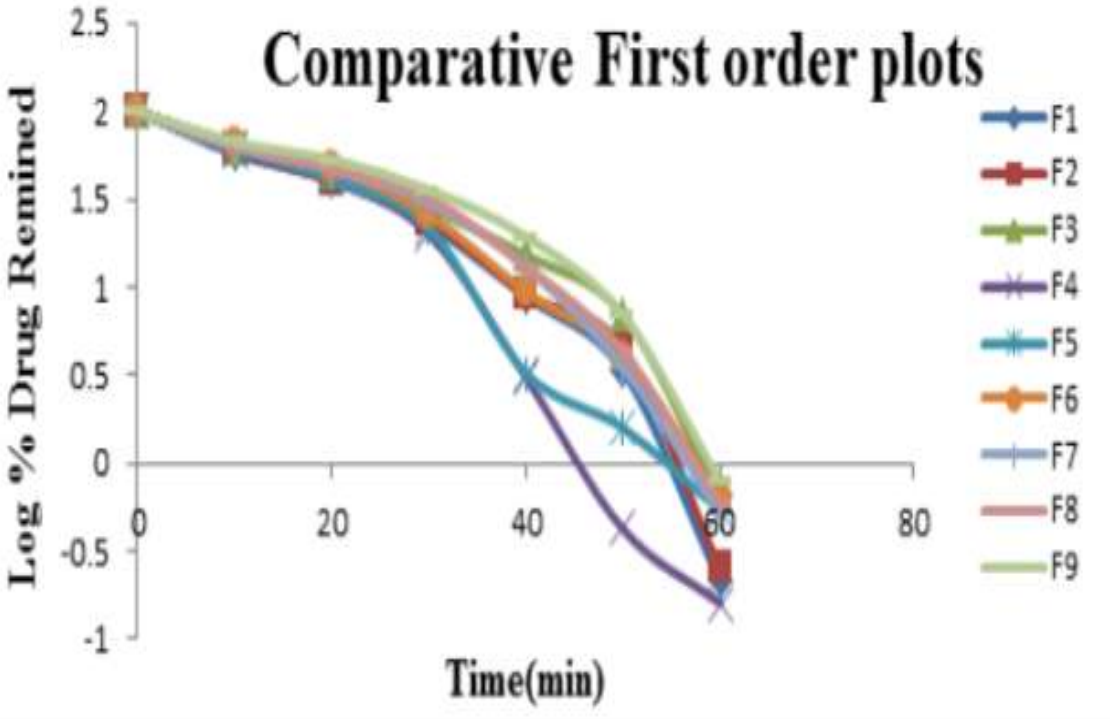
8	F8	8.797	1.337	29.232
9	F9	9.668	1.47	32.127
10	Lamictal-25	5.914	0.899	19.653

Design, formulation and characterization of oral disintegrating tablets for lamotrigine



Comparative zero order plots



comparative first order plots

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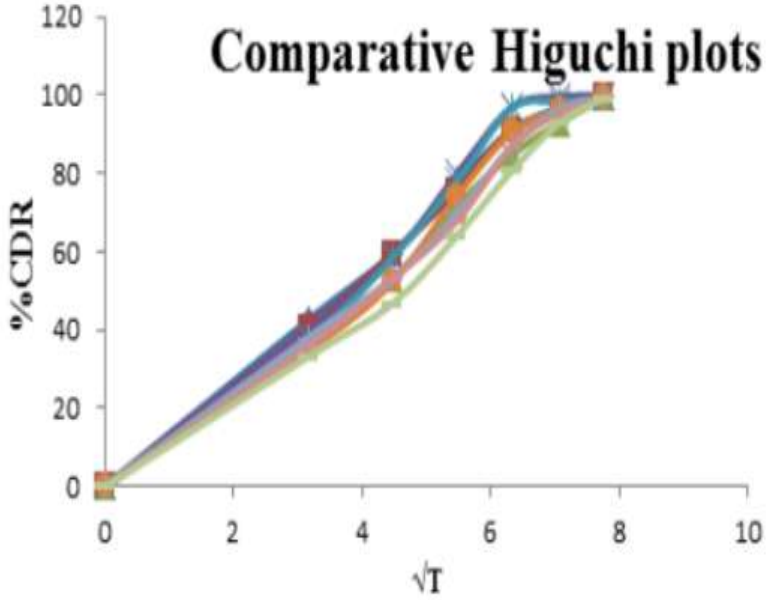
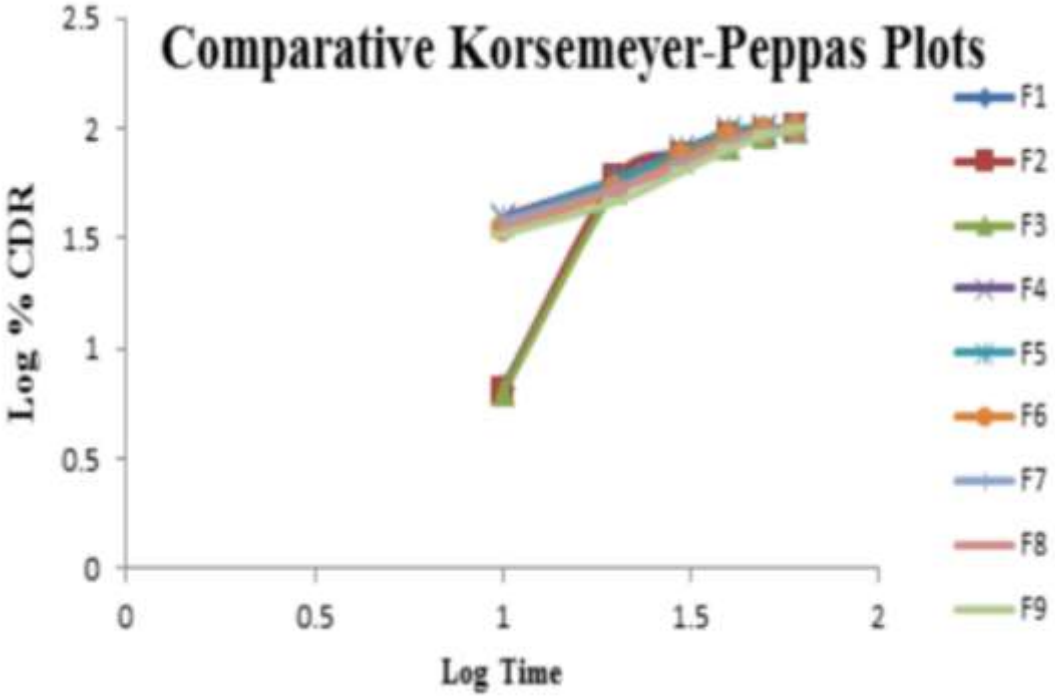


Comparative Higuchi plots



Comparative Korsmeyer-Peppas plots

III. CONCLUSION:

Considering data suggesting poor outcomes for individuals who struggle with chronic, impulsive ED symptoms and affective dysregulation, identifying potential treatments that can serve as an adjunct or alternative to existing interventions is a critical endeavour. In the current study, we explored the effect of lamotrigine as an

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adjunctive treatment to intensive DBT for EDs in individuals who struggled with impulsivity and affective lability. Despite limitations of the study design, our results provide tentative support for the use of lamotrigine in patients with binge-purge EDs, concurrent BPD features, and high levels of emotion dysregulation. Moving forward, future work should make use of randomized designs and matched control groups to pursue more definitive tests of lamotrigine as a promising treatment. The current research investigation focuses about influence of utilization of super disintegrants such as cross povidone and sodium starch glycolate in the formulation development of oral disintegrating tablet formulation of lamotrigine. results reveals that quantities of super disintegrants shows good impact on release of drug from formulation (directly proportional) the optimized formulation followed Higuchi's kinetics while the drug release mechanism was found to be Non-Fickian Diffusion, first order release type .On the basis of evaluation parameters ,the optimized formulation F5 may be used for the effective management of Epilepsy,convulsions.these may improve the patient compliance by showing rapid action via disintegration without difficult in swallowing and side effects which will ultimately improve therapeutic outcome .we could be able to minimize the oral cost of the formulation.

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