Effect of Superdisintegrants on the Enhancement Dissolution Characteristics for Lamotrigine

Raghavendra Kumar Gunda¹* and Prasad Rao Manchineni²

¹Department of Pharmaceutics, M.A.M college of Pharmacy, India

²Department of Pharmaceutical Analysis, M.A.M college of Pharmacy, India

*Corresponding author: Raghavendra Kumar Gunda, Department of Pharmaceutics, M.A.M college of Pharmacy, India

Abstract

The purpose of present investigation to study the effect of various superdisintegrants on the dissolution characteristics of Lamotrigine by formulating oral disintegrating tablets (ODT). Lamotrigine, an antiepileptic agent, belongs to type –II as per Biopharmaceutical Classification System (BCS) exerts Low aqueous solubility and high permeability behavior. ODT formulations of Lamotrigine were prepared using different quantities of Sodium Starch Glycolate (SSG) & Crospovidone (CP) employed as Superdisintegrants by Direct Compression technique as per 32 Factorial Design. Nine trials were formulated by considering amount of Crospovidone (X1), amount of SSG (X2) as Independent variables. The developed Formulations were evaluated for Pharmaceutical Product Performance. The t10%, t50%, t90%, Wetting time, Disintegration time were taken as Dependant variables. Results shows that all the formulations were lie within the acceptance criterion and the In-vitro dissolution profiles were subjected to kinetic modeling. The Polynomial equations were derived for dependant variables and are verified for validity by formulating Countercheck trials.

Conclusion: Formulation (F4) containing 35 mg of Sodium Starch Glycolate & 40 mg of Crospovidone was found to be best one among all and also similar to the Marketed product (LAMICTAL-25) (f2= 73.17, f1= 3.65 & No significant difference, t= 0.0218) to marketed product.

Keywords: Lamotrigine; Super disintegrates; Crospovidone; Sodium starch glycolate; Sodium; Wetting time; Disintegration time; Non-Fickian diffusion

Abbreviations: ODT: Oral Disintegrating Tablet; SD: Solid Dispersion; PEG: Poly Ethylene Glycol; CP: Crospovidone; SSG: Sodium Starch Glycolate; X1: Amount of Crospovidone; X2: Amount of Sodium Starch Glycolate; mg: milligram; mL: milliliter; IPQC: In-Process Quality Control; % CDR: Percentage Cumulative Drug Release; RPM: Revolutions per minute; BCS: Biopharmaceutical Classification System; UR: Un Released; Min: Minute; ºC: Degree Centigrade; mm: millimeter; t50%: Time taken to release 50% drug from dosage form; t90%: Time taken to release 90% drug from dosage form; WT: Wetting time; DT: Disintegration time dissimilarity factor; f1: Dissimilarity factor; f2: Similarity factor

Introduction

Swallowing is troublesome issue in situations like Dysphagia, specifically for both pediatrics and geriatrics. Oral disintegrating tablets created a new benchmark in the pharmaceutical trade. Porous tablets, rapimelts, Oro dispersible tablets, mouth-dissolving tablets, Fast dissolving tablets, quick dissolving, melt-in mouth tablets were used frequently in the place of ODT [1].

They rapidly disintegrate/dissolve in oral cavity within (<) 1min [2-4]. They were prepared by various techniques; formed ODTs show differences in sensual characteristics such as mouth feel, swallowability and taste. They also show variations in product performance like mechanical strength of tablet, drug release, bioavailability & stability. Manufacturing methods employed for formulating ODTs include mass extrusion, spray drying, cotton candy process, lyophilization, molding, compaction (wet & dry granulation, direct compression), patented technologies (Durasolv®, Orosolv®) [5-7].

Lamotrigine is an anti-epileptic drug and it is approved in the united states for the treatment of partial seizures and bipolar disease, belongs to class-II under BCS Classification and exhibit oral Bioavailability of about 98%. It is available as immediate release and sustained release formulations in the market with different strengths such as 25mg, 50mg and 100 mg. In 2009 GSK received FDA approval for extended release version of Lamotrigine (Lamictal-XR) [8-14].

To design an optimized formulation with an appropriate dissolution rate in a short time period with minimum heuristics is critical for Formulation Scientist. Response surface methodology (RSM) is used when only a few significant factors are involved in experimental optimization. The technique requires less experimentation and time, thus proving to be far more effective and cost-effective than the conventional methods of formulating dosage forms [3,9,12]. In the current research investigation the direct compression method was utilized to formulate tablets, due to numerous advantages such as simplest and cost effective tablet production method [15].

Materials and Methods

Lamotrigine was a gift sample procured from Meditech Pharma Pvt Ltd, Hyderabad, India. Mannitol, Crospovidone, Sodium Starch Glycolate were procured from SD Fine Chemicals, Mumbai. Other excipients were procured from LobaChemie Ltd, Mumbai.

Formulation development

Preparation of lamotrigine solid dispersion: PEG 6000 was melted in a beaker on a water bath maintained at 50- 60 °C. Required amount (D:E in 1:1) of the drug was then added to molten PEG 6000 and mixed thoroughly for 5min. The molten mixture was cooled rapidly by placing it in an ice bath for about 5min and solidified. The hardened mixture was powdered, sieved through #80, packed and stored in desiccators for further processing [9-10].

Preparation of lamotrigine fast dissolving tablets: Lamotrigine Tablets were prepared by direct compression method as per 32 factorial design. Experimental design was presented as Table 1. The formulae for the preparation of ODT were presented as Table 1. All ingredients were screened using #40 and mixed for obtaining uniform fine blends. Lubricants were screened through #80, mix them with above mixture and compressed to get ODT with the help of Tablet minipress (8 station) using 8mm circular punches. Obtained tablets were subjected to IPQC tests. Final tablets were transferred to airtight, light resistance containers for storage and further processing.

Where X1 means amount of Cospovidone and coded values as -1= 30 mg, 0=40mg, +1= 50mg.

X2 means amount of Sodium Starch Glycolate and coded values were-1= 25mg, 0=30mg, +1= 35mg.

Evaluation of Lamotrigine Fast Dissolving Tablets

Hardness

It was carried out with the help of Monsanto Tablet Hardness Tester [16].

Friability

The friability of the tablets was determined with the help of Roche Friabilator. Weight of 20 Tablets noted as Initial weight (W0) are dedusted in a drum for 4 min with a rotation rate of 25rpm and weight was noted as Final weight (W). Percentage friability was determined from following equation. The weight loss should not be more than 1 % [16].

Friability (%) = (W0- W) / W0 x 100

Content uniformity

20 tablets were randomly selected, and the percent drug content was determined, the tablets contained not less than 92.5% or not more than 107.5% (100±7.5%) of the labeled drug content can be considered as the test was passed [9,17].

Assay

Select fixed number of sample on the random basis (20), comminute them to a obtain powder. The powder equivalent to 100mg Lamotrigine was weighed and transferred to 100mL volumetric flask containing 60mL of methanol and sonicated for 10min to solubilize the drug completely then dilute the methanolic solution with water to make up the final volume. From that prepare further dilution of 2mL aliquot in 100mL of 0.1 N HCl. The obtained solution was filtered through Whatman filter paper and absorbance of solution as measured at 254nm with the help of UV-Visible spectrophotometer [9].

Thickness

Thickness was determined with the help vernier calipers [18].

Wetting time

To measure Wetting time of the Tablet, a piece of Tissue paper folded twice was placed in a small petri dish (Internal Diameter is= 6.5cm) containing 5ml of Distilled water. A Tablet placed on the paper, and the time for complete wetting of the tablet was measured in sec [15-18].

In-vitro dissolution study

Lamotrigine oral disintegrating tablets subjected to dissolution test with the help of USP XXIII type-II tablet dissolution test apparatus using 900ml of 0.1N HCl operated under standard set of conditions. Withdraw samples at fixed intervals with the aid of syringe with a pre-filter and maintain the sink condition. Absorbances for samples were noted at 254nm using UV Visible spectrophotometer (after suitable dilutions if necessary). The determinations were performed in triplicate (n=3) [9].

Disintegration test

Disintegration of oral disintegrating tablets is achieved in the oral cavity owing to the impact of saliva, salivary volume is limited hence there is no proper In vitro In vivo correlation (IVIVC) was found in USP and IP. A modified method was used to determine to perform the disintegration test. A cylindrical vessel with 10 # was placed in such way that only 2ml of medium would be placed below the sieve. 6ml of medium was placed inside the vessel in such way that 4ml of the media was below the sieve and 2ml above the sieve. Tablet was placed on the sieve and the whole assembly was then placed on the top of agitator. Disintegration time was recorded. Six tablets were chosen randomly from the composite samples and the average value was determined [18].

Kinetic modeling of drug release

The dissolution profile of all the formulations was subjected to kinetic modeling [19-23].

Results and Discussion

9 Lamotrigine Oral Disintegrating Tablet formulations were prepared by direct compression method using various proportions of super disintegrates combination as per 32 factorial design and the formulae presented in Table 1. All the formulations containing

25mg of Lamotrigine (as Lamotrigine SD with PEG as 1:1 ratio) prepared tablets prepared and evaluated for various pharmacopeial limits such as, drug content, mean hardness, friability, mean thickness, Weight variation as per official methods. Results shows that all the formulations were lie within the acceptance criterion; complete profile for finished product evaluation was presented as Table 2.

Table 1: Experimental Design for the Formulation of Lamotrigine Fast Dissolving Tablets.

Formulation Code	X_1	X_2
F_1	1	1
F_2	1	0
F_3	1	-1
F_4	0	1
F_5	0	0
F_6	0	-1
F_7	-1	1
F_8	-1	0
F_9	-1	-1
C_1	-0.5	-0.5
C_2	0.5	0.5

Table 2: Formulae for the Preparation of Lamotrigine Fast Dissolving Tablets.

Name of Ingredients	Quantity of Ingredients per each Tablet (mg)								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Lamotrigine SD (Complex)	50	50	50	50	50	50	50	50	50
Mannitol	59	64	69	69	74	79	79	84	89
Crospovidone (X_1)	50	50	50	40	40	40	30	30	30
Sodium starch glycolate (X_2)	35	30	25	35	30	25	35	30	25
Colloidal Silicone dioxide	3	3	3	3	3	3	3	3	3
Magnesium Stearate	3	3	3	3	3	3	3	3	3
Total Weight	200	200	200	200	200	200	200	200	200

From the results of wetting time and Disintegration time, it reveals that as the concentration of super disinterants increases the wetting time decreases (Concentration of superdisintegrants inversely proportional to wetting time). Wetting time for all the formulations varied from 23.11±2.3 to 30.5±1.81sec. The

Disintegration Time of tablets was in the range of 22.5±1.7-35.5±1.34sec. Plots for wetting time and disintegration was presented as (Figure 1&2). The cumulative percentage drug released by each tablet in the *In Vitro* Release studies were based on the mean content of the drug present in the respective tablet.
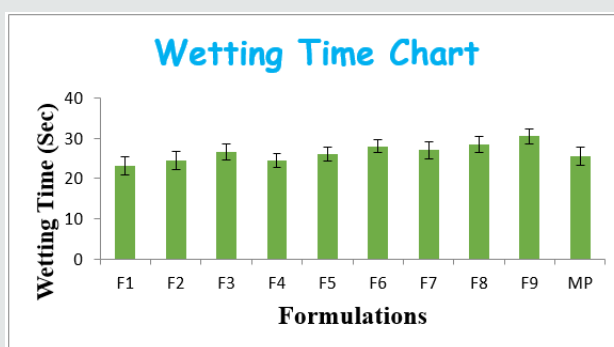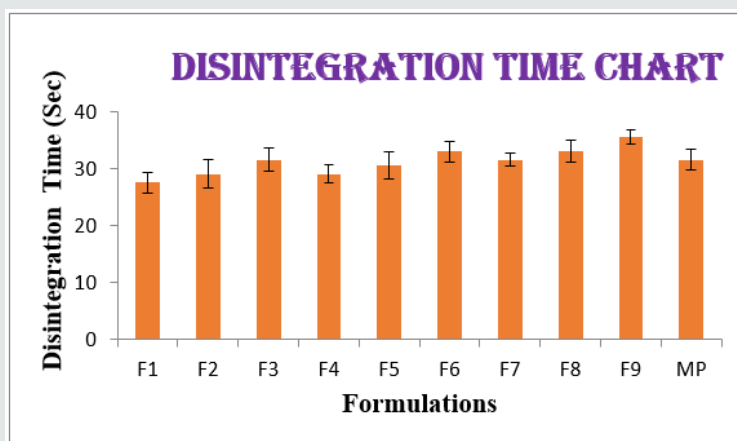

Figure 1: Wetting Time Chart.

Figure 2: Disintegration Time Chart.

Cumulative % Drug release for F1-F9 at 60min was found to be in the range of 99.21±0.66-99.84±0.01%. Dissolution profiles of Lamotrigine ODT were subjected to goodness of fit test by linear regression analysis according to kinetic modeling to ascertain the drug release mechanism. The statistical parameters for kinetic models were determined and data present as Table 3 & 4 and plots represented as Figure 3-6 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 ranges from 0.492-0.643 that shows Non-Fickian diffusion mechanism. Polynomial equations were developed for dependent variables such as t10%, t50%, t90%, Wetting time, Disintegration time. The validity of developed equations was verified by preparing counter check formulation (C1, C2). Results for counter check formulations presented Table 5. Response morphological plots shown in Figure 7-11.
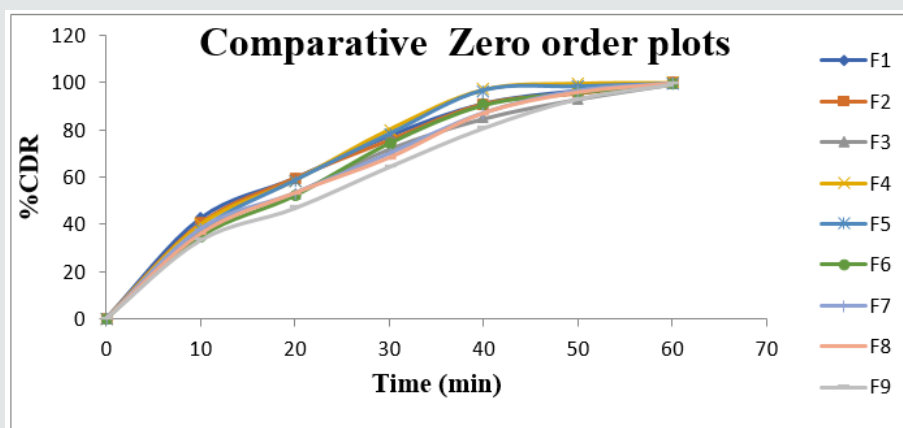
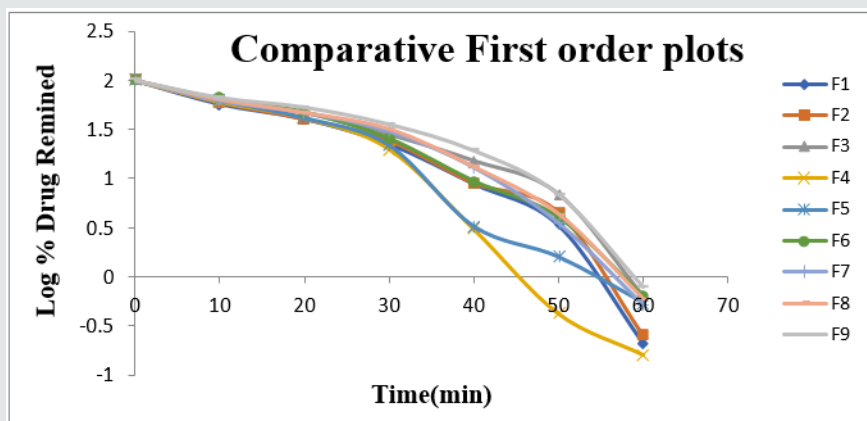

Figure 3: Comparative Zero order plots.
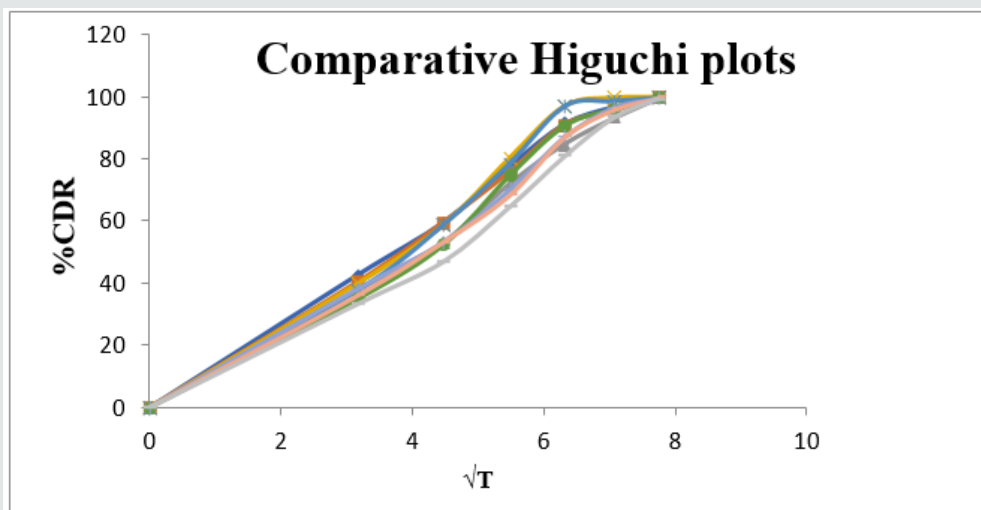

Figure 4: Comparative First order plots.

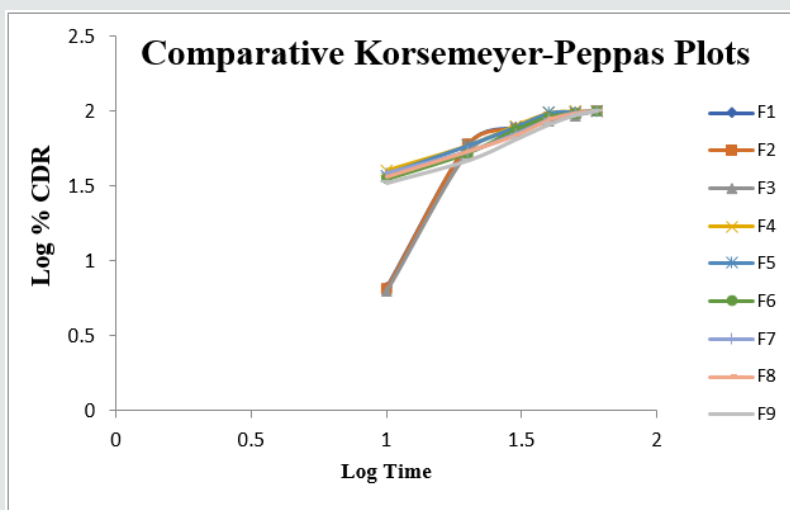**Figure 5:** Comparative Higuchi plots.

Figure 6: Comparative Korsmeyer-Peppas plots.
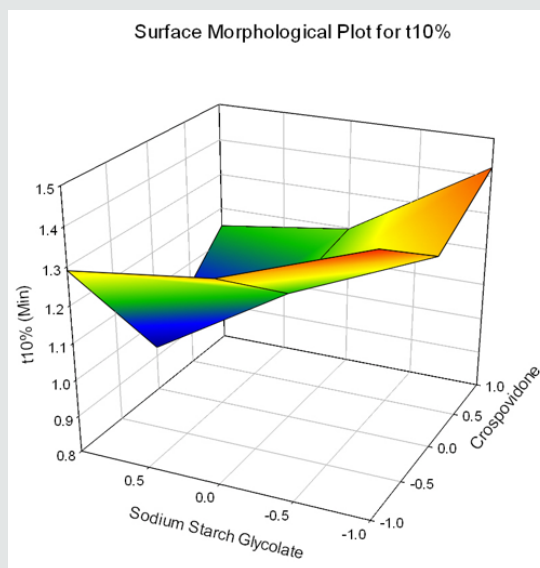

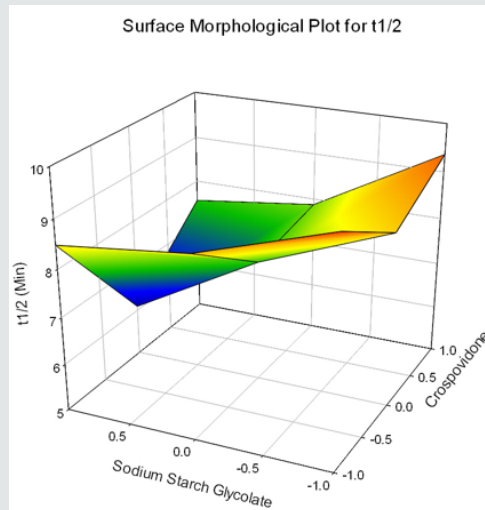**Figure 7:** Surface morphological plot for Disintegration t_{10}%.

Figure 8: Surface morphological plot for Disintegration t_{50}%.
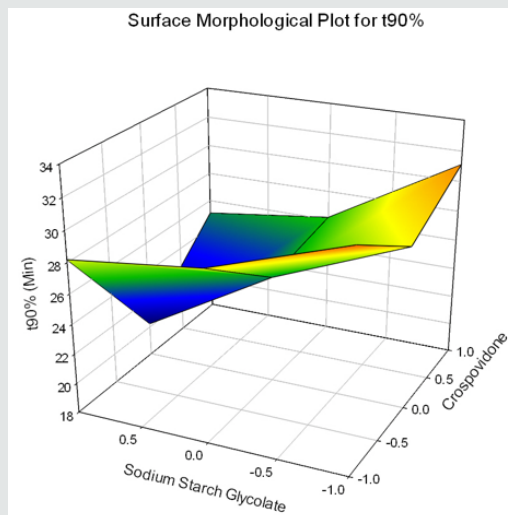

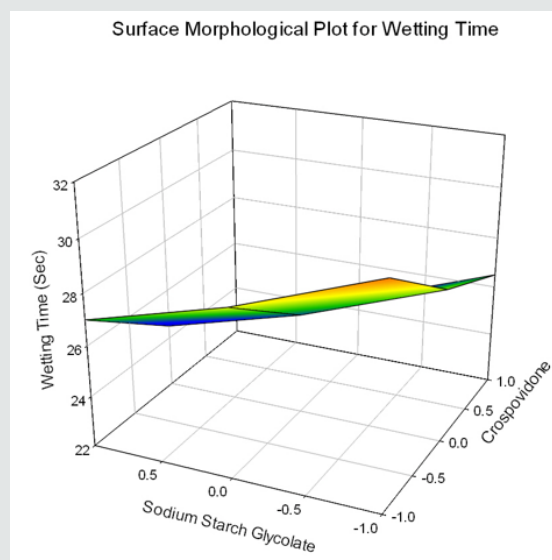**Figure 9:** Surface morphological plot for Disintegration t_{90}%.

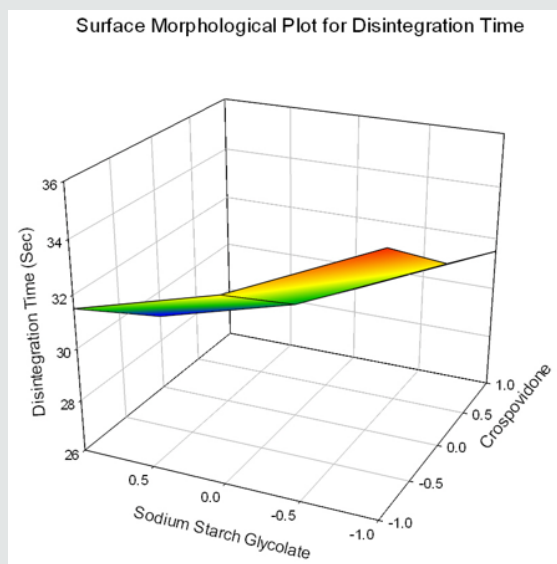**Figure 10:** Surface morphological plot for Wetting Time.

Figure 11: Surface morphological plot for Disintegration Time.

Table 3: Post-Compression Parameters.

S. No	Formulation Code	Hardness (kg/cm)	Thickness (mm)	Friability (%)	Average Weight (mg)	Drug Content (%)	Wetting Time (sec)	Disintegration Time (sec)
1	F_1	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	F_2	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	F_3	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	F_4	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	F_5	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	F_6	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	F_7	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	F_8	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	F_9	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

Table 4: Dissolution/ Kinetic parameters.

| S.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	F_1	19.656	1.569	0.941	2.269	0.04	0.936	0.669	13.499	0.996	1.132	0.502	0.992
2	F_2	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	F_3	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	F_4	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	F_5	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	F_6	14.757	1.638	0.959	2.225	0.035	0.961	3.422	13.76	0.991	0.928	0.621	0.989
7	F_7	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	F_8	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	F_9	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

Table 5: Dissolution/ Kinetic parameters.

| S.NO | Formulation Code | Kinetic Parameters | | |
		t1/2 (min)	t10% (min)	t90% (min)
1	F_1	7.547	1.147	25.08
2	F_2	7.873	1.197	26.162

3	F_3	9.364	1.423	31.117
4	F_4	6.091	0.926	20.24
5	F_5	7.588	1.153	25.217
6	F_6	8.664	1.317	28.79
7	F_7	8.484	1.29	28.192
8	F_8	8.797	1.337	29.232
9	F_9	9.668	1.47	32.127
10	Lamictal-25	5.914	0.899	19.653

$Y1 = 1.251 - 0.055X1 - 0.141X2 - 0.024X1X2 + 0.178 X1^2 + 0.332X2^2$ (for $t_{10}\%$)

$Y2 = 8.231 - 0.361X1 - 0.929X2 - 0.158X1X2 + 1.175 X1^2 + 0.217X2^2$ (for $t_{50}\%$)

$Y3 = 27.351 - 1.199X1 - 3.087X2 - 0.525X1X2 + 3.903 X1^2 + 0.721X2^2$ (for $t_{90}\%$)

$Y4 = 26.512 - 1.982X1 - 1.732X2 + 0.518 X1^2 + 0.268 X2^2$ (for Wetting Time)

$Y5 = 31.167 - 2X1 - 2 X2 + 0.5 X1^2 + 0.5 X2^2$ (for Disintegration Time)

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, t10% = 0.926min, t50% = 6.091min, t90% = 20.240min). The final best Formulation F4 is compared with Marketed product (LAMICTAL-25) tablets and Comparative Dissolution profiles shown in Figure 12. Which shows similarity (f2= 73.17, f1= 3.65).
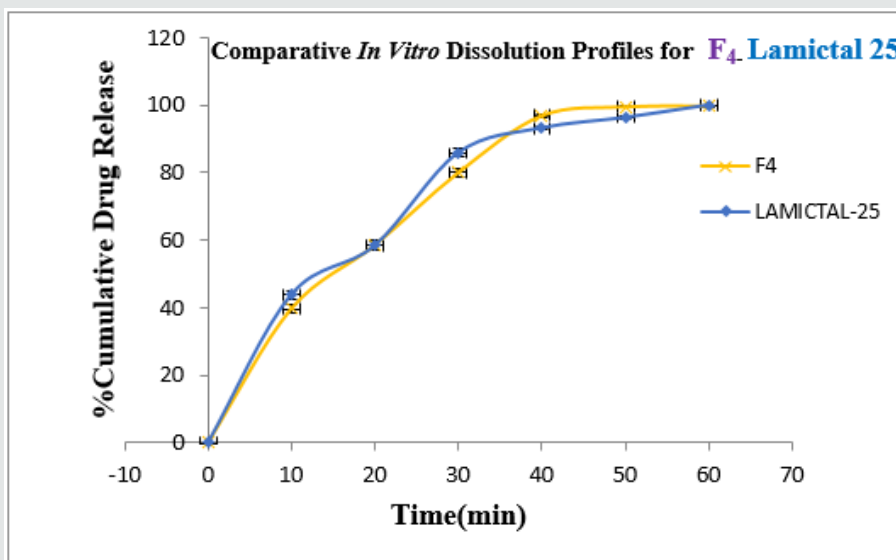

Figure 12: Comparative In-vitro Dissolution Profiles of F4, LAMICTAL.

Conclusion

The current research investigation focuses about influence of utilization of superdisinterants such as Crospovidone and Sodium Starch Glycolate in the formulation development of oral disintegrating tablet formulations of Lamotrigine. Results reveals that quantities of Superdisintegrant 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 F4 may be used for the effective management of Epilepsy, convulsions. This may improve the patient compliance by showing rapid action via disintegration without difficult in swallowing and side effects which will ultimately improve the therapeutic outcome. We could be able to minimize the per oral cost of the Formulation (Table 6).

Table 6: Kinetic parameters for counter check formulations.

| Formulation code	Predicted value					Actual observed value				
	t10% (min)	t50% (min)	t90% (min)	WT (Sec)	DT (Sec)	t10% (min)	t50% (min)	t90% (min)	WT (Sec)	DT (Sec)
C_1	1.471	9.185	30.52	28.57	33.417	1.48	9.21	30.78	27.79	33.25
C_2	1.275	7.895	26.233	24.852	29.417	1.32	7.92	26.45	24.35	28.98

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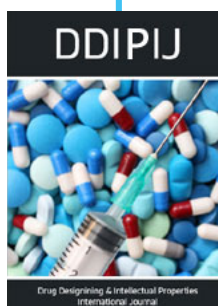
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