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FORMULATION AND IN-VITRO EVALUATION OF FAST DISSOLVING TABLETS OF LEVETIRACETAM USING RESPONSE SURFACE METHODOLOGY

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ABSTRACT

The aim of present study was formulation and in-vitro evaluation of fast dissolving tablets of levetiracetam by using direct compression technique. levetiracetam fast dissolving tablets was formulated with varying concentrations of superdisintegrants like Crosscarmellose sodium (CCS) and Sodium starch Glycolate using Design Expert®DX 10.0.7.0 license version software. All the formulation batches were prepared by direct compression method using rotary tablet compression machine using flat punch. The prepared tablets were evaluated for weight variation, hardness, thickness, friability, disintegration time, drug content, moisture absorption and dissolution rate study. The tablets show acceptable weight variations as per pharmacopoeial specifications. Friability shows below 1% indicating a good mechanical resistance of tablets. All the FDTs prepared disintegrated within 2 min 50 sec. Among the superdisintegrants Croscarmellose sodium gave rapid disintegration of the tablets.

INTRODUCTION

Dysphasia is a common problem associated with the tablets and capsule which results in high degree of noncompliance. Many conventional solid oral dosage forms, are available which releases the drug instantly to obtained fast and complete systemic drug absorption in mouth itself.[1]Solid dosage forms that can be disintegrated, dissolved, or suspended by saliva in the mouth resulting in easy swallowing can provide significant benefits to the pediatric and geriatric population, as well as other patients who prefer the convenience of easily swallow able dosage forms. This tablet disintegrates instantaneously when placed on tongue, releasing the drug that dissolves or disperses in the saliva.[2]Characteristic advantages which make fast dissolving tablet popular are administration without water, patient compliance, dose precision and quick onset of action. This type of system allow drug to avoid the first pass metabolism and ultimately improvement in bioavailability.[3] Fast dissolving tablets are designed to increase the bioavailability of the geriatric patient who are suffering from swallowing of solid dosage form orally, poorly soluble drugs. These are conveniently administrable to the pediatric and geriatric patient. Fast

dissolving tablet characterized by disintegrating or dissolving in the mouth within one minute some within seconds, theyliquefy on the tongue and the patient swallows the liquid.A number of techniques are used to prepare fast dissolving tablet. These tablets are prepared using very water soluble excipient. The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety. The new business opportunity like product differentiation, product promotion, patent extension, and life cycle management become easy after the intervention of FDTs. The FDTs are often formulated for existing drugs with an intention to extend the patent life of the drug through product differentiation.[4] Levetiracetam is an anticonvulsant agent, used to treat epilepsy. It is used for partial onset, myoclonic or tonic clonic Seizures. It works by decreasing abnormal excitement in the brain.Hence a rapid onset of action is required which can be achieved by rapid dissolution and absorption of drug. In the current research investigation the direct compression method was utilized to formulate tablets by optimizing the formulation through response surface methodology due numerous advantages such as simplest and cost effective tablet production method.

MATERIALS AND METHOD

Levetiracetam Lupin,Nagpur,Sodium Starch Glycolate Loba chemicals, Mumbai,Cross carmelose Sodium Research-lab-Fine chemical industry,Talc Lobachemicals, Mumbai, Magnesium Stearate Himedia,Mumbai , Microcrystalline Cellulose Lobachemicals,Mumbai. All other chemicals were of analytical grade.

Preparation of Levetiracetam Fast Dissolving Tablets:

Fast dissolving tablets of Levetiracetam were prepared by direct compression method using 3^2 factorial design. All the ingredients (as shown in table 2) were powdered separately and passed through sieve no. 40 separately. The drug and directly compressible excipient 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, in an inflated polyethylene pouch magnesium stearate and talc were added last and mixed for further two minutes and the tablets were compressed using 8-12 mm flat round punches to get tablets of 250 mg weight.

Experimental design (3^2 full factorial design)

To investigate the efficiency, a three-level, 3^2 full factorial design was constructed with no centre points. Two variables were chosen, namely, concentration of SSG (Mg) ($X1$), concentration of CCS (Mg) ($X2$). Each independent variable had 3 levels which were coded as –1, 0 and +1 i.e. concentration of SSG(Mg) (2mg,4mg,6mg), concentration of CCS(Mg) (2mg,4mg,6mg). 9 runs were carried out in order to obtain optimised formulation.

Statistical analysis and optimization of formulation using RSM

Design was used for the generation and evaluation of statistical experimental design. Response surface modelling and evaluation of the quality of fit of the model for the current study were performed employing Design Expert®DX 10.0.7.0 license version software Polynomial models including linear, interaction and quadratic terms were generated for all the response variables using multiple linear regression analysis (MLRA). A second-order polynomial equation that describes the effect of independent factors on the response is expressed in the following forms:

$$\text{Quadratic model} = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2$$

Where Y is the dependent variable; β_0 is the arithmetic mean response of the nine runs and β_i (β_1; β_2; β_{12}; β_{11} and β_{22}) is the estimated coefficient for the corresponding factor X_i (X_1, X_2, X_1X_2, X_1X_1 and X_2X_2). The main effects (X_1 and X_2) represent the average result of changing one factor at a

time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. The equations enable the study of the effects of each factor and their interaction over the considered responses. The polynomial equations were used to draw conclusions after considering the magnitude of coefficients and the mathematical sign they carry, i.e. positive or negative.

Evaluation of Levetiracetam Fast Dissolving Tablets

Hardness: The hardness test was performed using Monsanto Tablet Hardness Tester.[5]

Friability: The friability of the tablets was determined with the help of Roche Friabilator. Weight of 20 Tablets noted as Initial weight (W1) are dedusted in a drum for 4 min with a rotation rate of 25rpm and weight was noted as Final weight (W2). Percentage friability was determined from following equation. The weight loss should not be more than 1%.

Friability = [(Initial weight (W1) - Final weight (W2))/(Initial weight (W1) X 100

Uniformity of content: 20 tablets were randomly selected and the percent drug content was determined, an accuratelyweighed quantity of powder equivalent to 10mg of Levetiracetam was taken into 100 ml volumetric flask, dissolved in phosphate buffer of pH 6.8 and the solution was filtered through whatman filter paper no.41. The filtrate was collected and suitably diluted with phosphate buffer of pH 6.8. The drug content was determined at 215 nm. 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.[5]

Thickness: Thickness of tablets was determined using Vernier Caliper (Indian Caliper Industries, Ambala, India). Three tablets from each batch were used, and an average value was calculated.[6]

Disintegration Test: The test was carried out on 6 tablets using single unit disintegration testapparatus (Make: Paramount) digital tablet disintegration tester (Veego, India) Disintegration time of the tablets wasdetermined employing Distilled water as a disintegration mediaat 37°C ± 2°C, and the time taken for complete disintegration of the tablet with no profound mass remaining in the apparatus was measured in seconds.

Water Absorption Ratio: A piece of tissue paper folded twice wasplaced in a small Petri dish containing 6 ml of water. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was then weighed. Water absorption ratio, R was determined using following equation.[7]

$R = 100 \times (Wa – Wb)/Wa$

Where,

Wa = Weight of tablet after water Absorption

Wb = Weight of tablet before water absorption.

Dispersion Time:Tablets were added in 10 ml of phosphate buffer pH 6.8 at 37 0 ± 0.5 0C. Time required for complete dispersion ofthe tablet was measured [6].

Dissolution Rate Study: The release of formulated FDTs was determined using USP eight-stage dissolution testing apparatus-2 (paddle method) (LABINDIA, DISSO 8000). The dissolution test was performed using 900 mL of phosphate buffer solution, pH 6.8 at 37 ± 0.5∘ C and 50 rpm. A sample (5 mL) of the solution was withdrawn from the dissolution apparatus at specific time intervals, and the samples were replaced with fresh dissolution medium. The samples were filtered through Whatman filter paper. Absorbance of these solutions was measured at 215 nm using a double beam UV spectrophotometer (UV-1800 Shimadzu). Cumulative percentage (%) of drug release was calculated using standard plot of levetiracetam.[5]

Kinetic modeling of drug release: The dissolution profile of all the formulations was subjected to kinetic modeling using PCP disso Software EXCEL 2007.[5]

RESULT AND DISCUSSIONS:

Analysis of data by Design Expert software:

A 3^2 full factorial design was selected and the 2 factors were evaluated at 3 levels, respectively. The concentration of SSG(Mg) ($X1$), concentration of CCS (Mg)($X2$) were selected as independent variables and the dependent variables were Hardness and

Optimization (Model Validation)

The process was optimized for the response hardness and disintegration time. The results clarified an optimum setting for fast dissolving tablet and relating counter plots and response surface diagrams are indicated clearly in figure 1. To verify the reproducibility, the Hardness kg/cm$^{2\ of}$ 3.92 and Disintegration time in sec at 47.7 was formulated as shown in table 5. The formulations were evaluated for response study and the results (table 5) showed a good relationship between the experimental and predicted values, which confirms the practicability of the model.

Data Analysis by Design Expert Software

The 3^2 full factorial design was selected to study the effect of independent variables concentration of SSG(Mg) ($X1$), concentration of CCS(Mg)($X2$) on dependent variables hardness and disintegration time . A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses.

$$Y=b_0+b_1 X_1+b_2 X_2+b_{12} X_1X_2+b_{11}X_1^2+b_{22}X_2^2$$

Where,

Y- Dependent variable

b_0 -arithmetic mean response of the nine runs and

b_i (b_1,b_2,,b_{12},b_{11} and b_{22})- estimated coefficient for the corresponding factor X_i (X_1,X_2,X_{12},X_{11},and X_{22}), which represents the average results of changing one factor at a time from its low to high value.The interaction term (X_1X_2) depicts the changes in the response when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity.

Disintegration. The data obtained were treated using Stat Ease Design Expert 10.0 software and analyzed .The data were also subjected to 3-D response surface methodology to study the interaction of concentration of SSG(Mg) ($X1$), concentration of CCS (Mg) ($X2$) on dependent variables. Summary of designs and responses is given in table no. 3and 4.

The responses of the formulations prepared by 3^2 factorial design batches are indicated. The data clearly indicate that values are strongly dependent on the selected independent variables. The fitted regression equations relating the responses hardness and disintegration time are shown in the following equations, respectively.

Final equations in Terms of Actual Factors:

Hardness=+7.87425-1.46458-0.45116+0.037500+0.16750+0.023265

Disintegration = +137.215419-70238-20.04082+1.14286+1.54167+1.60544.

9 batches of Levetiracetam fast Disintegrating Tablet formulations were prepared by direct compression method using response surface methodology (Design Expert®DX 10.0.7.0 license version software) presented in Table 1. All the formulations containing 215mg of Levetiracetam prepared tablets prepared and evaluated for various pharmacopoeial limits such as, drug content, mean hardness, friability, mean thickness, Weight variation as per official methods. The Thickness of tablet ranged from 2.4±0.7mm – 3.4±0.1mm mm, all the batches of tablets showed less deviation in thickness as mentioned in Table 6, hence Uniformity in thickness and diameter shows formulations were compressed without sticking to the dies and punches.The Hardness varied from 3.9±3.7 to 5.2±4.8 Percentage Friability of all batches range from and 0.1 – 0.96 % (within the limit <1%) which indicates the non-hindrance in disintegration and transportability respectively (Table 6). The Hardness and Percent Friability indicated good mechanical strength of the tablet. All the tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±5%.

Table 1:3^2 full factorial design with independent and dependent variable

Run	Factors (Independent variables)		Responses (Dependent variable)
	concentration of SSG(Mg)	concentration of CCS(Mg)	
1	1	0	Y_1 = HARDNESS(KG/CM^2) Y_2 = DISINTERGATION TIME(SECONGS)
2	1	-1	
3	0	1	
4	0	0	
5	1	1	
6	-1	0	
7	0	-1	
8	-1	1	
9	-1	-1	

Table 2: Composition of Fast Dissolving Tablet:

Name Of Ingredient	**Formulation Batches(Quantity In Mg)**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Levetiracetam	125	125	125	125	125	125	125	125	125
Sodium Starch Glycolate	2	4	6	2	4	6	2	4	6
Cross Carmelose Sodium	2	2	2	4	4	4	6	6	6
Talc	3	3	3	3	3	3	3	3	3
Magnesium Stearate	4	4	4	4	4	4	4	4	4
Micro Crystalline Cellulose	114	112	110	112	110	108	110	108	106
Total	250	250	250	250	250	250	250	250	250

Table no 3: Design Summary

Factor	**Name**	**Units**	**Type**	**Subtype**	**Minimum**	**Maximum**
A	SSG	MG	Numeric	Continuous	2	6
B	CCS	MG	Numeric	Continuous	2	9

Table no 4: Table no Response Summary

Response	**Name**	**Units**	**Observations**	**Analysis**	**Minimum**	**Maximum**	**Mean**
Y1	Hardness	Kg/cm^2	9	Polynomial	5.2	4.38	4.38
Y2	Disintegration	sec	9	Polynomial	98	63.77	63.77

Table 5.Comparison of Predicted and Experimental Values CSM

Responses	**CSM**	
	Predicted	**Experimental**
Hardness kg/cm^2	3.92	3.90±0.89kg/cm^2
Disintegration sec	47.7	48±2.1 sec

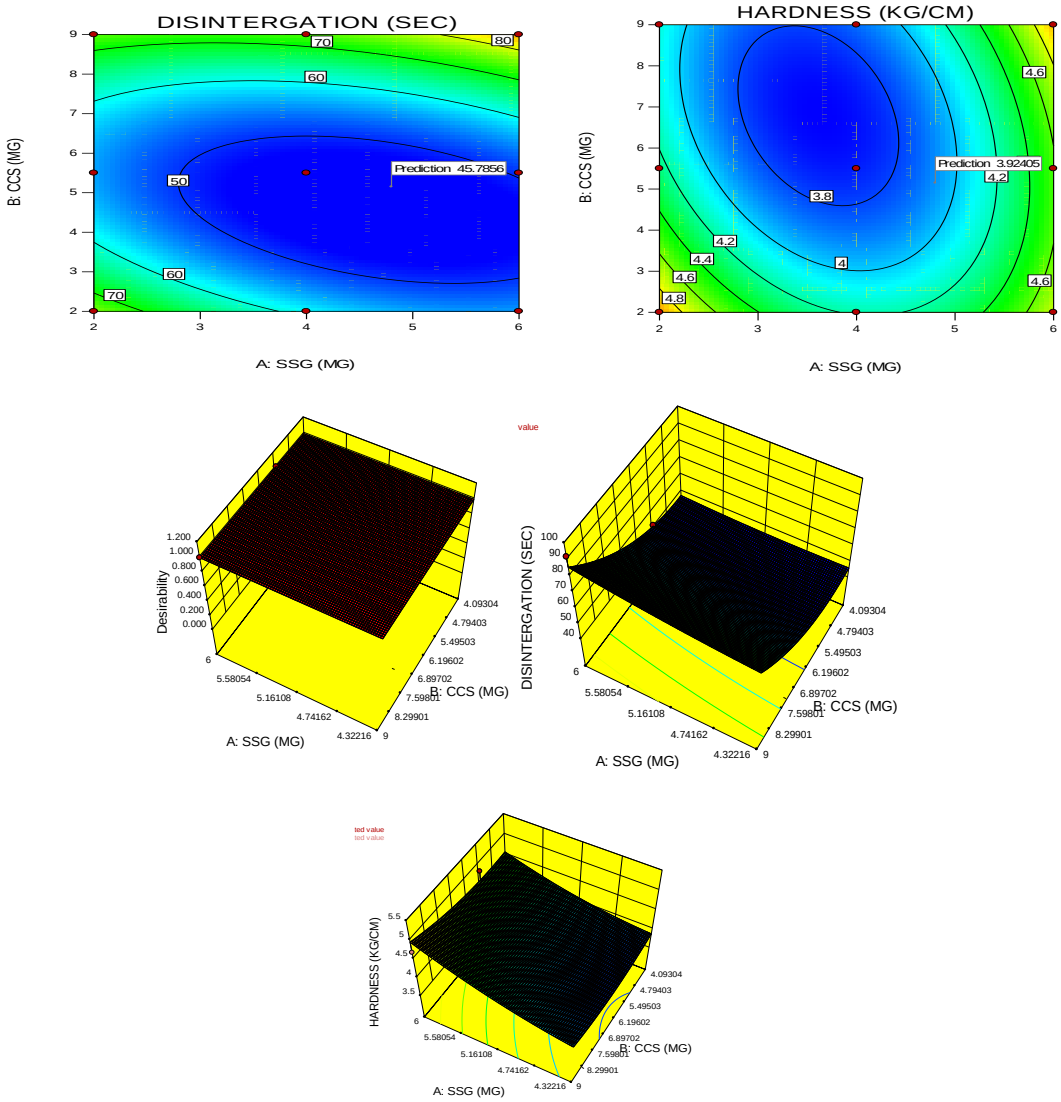


Figure 1: Response surface diagram indicating desirability and predicted value

Formulation Code	Post compression Studies							
	Avg. Wt. (g) (n=10)	Thickness (mm) (n=3)	Hardness (kg/ cm^2) (n=3)	%Friability	% Drug content	Disintegration Time (Sec)	Dispersion time (min)	Water absorption ratio %
F1	0.2375	2.50	5.2	0.96	98.1	70	1.15	0.13
F2	0.2226	2.50	4.07	0.47	98.2	52	0.50	44.11
F3	0.2436	2.4	4.05	0.54	99.8	82	1.25	98.8
F4	0.2407	3.47	4.2	0.41	86.30	60	1.52	94.6
F5	0.2479	2.99	3.9	0.13	88.38	70	1.36	96.4
F6	0.2471	3.20	4.7	0.80	86.3	92	1.13	88.9
F7	0.2443	2.83	4.8	0.81	94.4	48	1.29	89.2
F8	0.2506	3.03	4.8	0.50	96.5	51	1.38	92.8
F9	0.2484	2.79	3.7	0.87	99.8	49	1.27	98.6

Table 6: Post Compression Studies for Formulation of Fast Dissolving Tablets of Levetiracetam

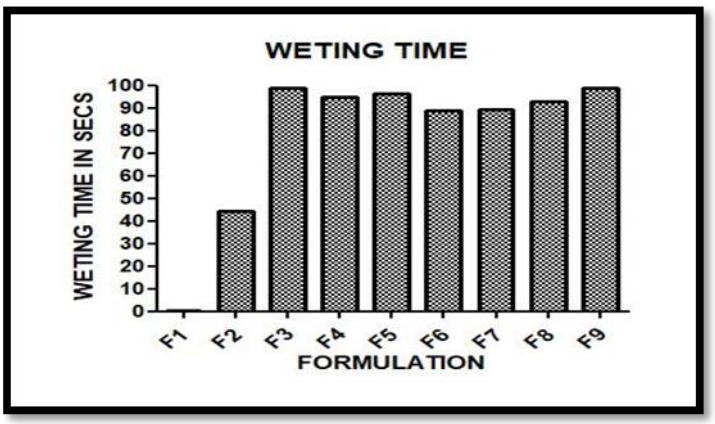
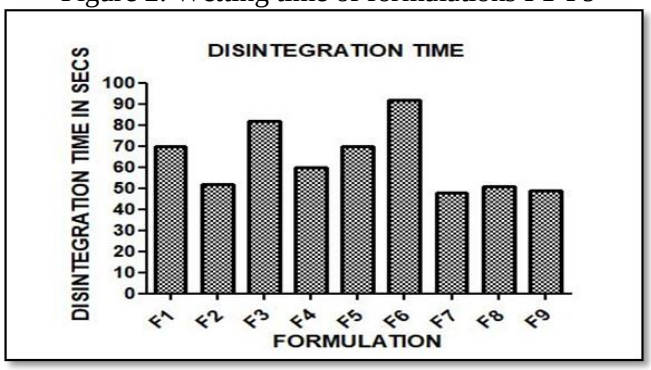


Figure 2: Wetting time of formulations F1-F9



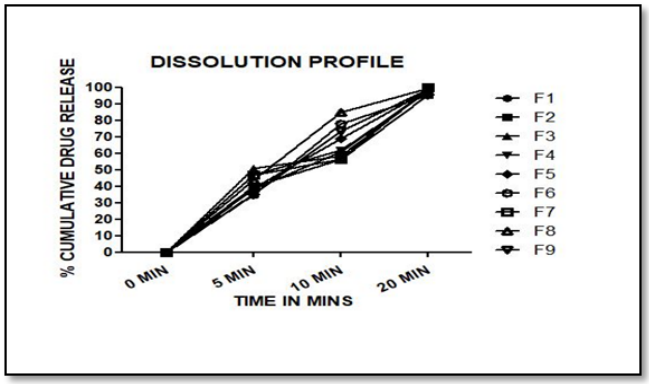


Figure 4: Dissolution profile of formulations F1-F9

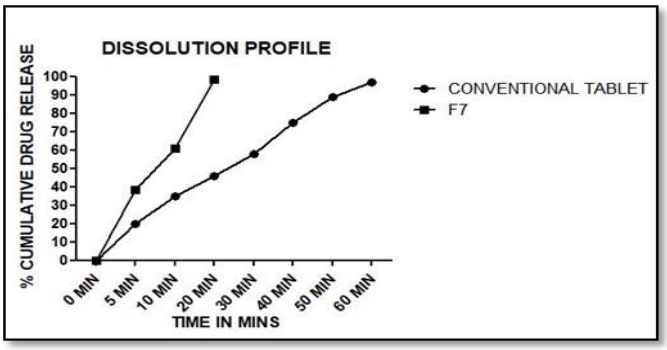


Figure 5: Comparison of dissolution profile of formulations F7 and conventional dosage form

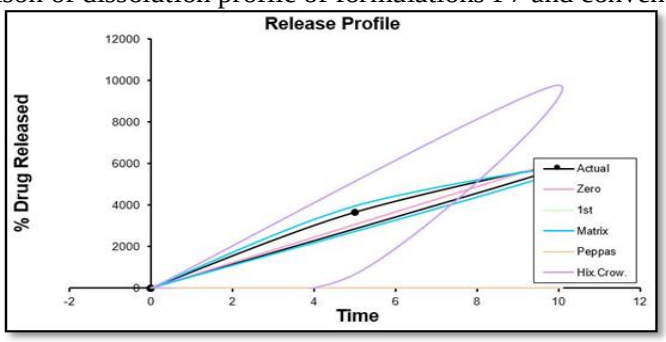


Figure 6: Model fitting for Formulations

Table 7: Release kinetics of fast dissolving Levetiracetam tablets

Formulation	Zero order kinetics		First order kinetics		Matrix kinetics		Hixon-Crowell		Kosermeyer-Peppas		
Code	R	K	R	k	R	k	R	k	R	k	N
F1	0.083	1.757	0.987	0.0015	0.9873	2.347	0.9755	3.5358	0.9528	0.0004	0.412
F2	0.0843	1.7292	0.9817	0.0015	0.9858	2.3683	0.9707	4.004	0.9422	0.0004	0.413
F3	0.0734	1.578	0.865	0.0012	0.882	2.0772	0.831	4.316	0.8311	-0.003	0.37
F4	0.085	1.7632	0.988	0.0017	0.9891	2.367	0.9811	3.534	0.9576	0.0004	0.42
F5	0.081	1.751	0.976	0.0014	0.9881	2.354	0.9821	3.234	0.952	-0.004	0.412
F6	0.0834	1.721	0.9812	0.0014	0.09854	2.354	0.9815	3.201	0.9489	-0.004	0.41
F7	0.085	1.7632	0.988	0.0017	0.9891	2.367	0.9811	3.534	0.9576	0.0004	0.42
F8	0.0843	1.7292	0.9817	0.0015	0.9858	2.3683	0.9707	4.004	0.9422	0.0004	0.413
F9	0.083	1.757	0.987	0.0015	0.9873	2.347	0.9755	3.5358	0.9528	0.0004	0.412

Average weight for all formulations was found to be in the range of 249.9±0.3 to 251.48±2.0mg. This is due to good flow property and compressibility of all the formulations. The tablets passed the USP limits. From the results of wetting time and Disintegration time, it reveals that as the concentration of superdisinterants increases the wetting time decreases (Concentration of superdisintegrants inversely proportional to wetting time). Percent Water absorption ratio was found to be within 98.6±0.54 and 44.11±0.13. Wetting time ranged from a minimum of 44.11±0.13 for F1 and maximum of 98.8±1.37 s for F3 as shown in Table 6.Drug content of fast disintegrating tablet of Levetiracetam was found to be between 85 and 99.8% as shown in Table 6. The Tablet pass the test if 9 of the 10 tablets must contain not less than 85% and not more than 115% of the labelled drug content and the 10th tablet may not contain less than 75% and more than 125% of the labelled content. Formulations F2 and F7 showed good disintegration and drug release at 10 minutes. The lowest disintegration time was 48 s for F7 and 52 s for F2 respectively and maximum % drug release at 20 minutes was obtained from F7 as shown in Table 6. The increase in concentration of Croscarmellose in F2 and F7 respectively promoted rapid swelling and thereby disintegration of the tablet into apparently minute particles .Results for all Post-compression parameters were tabulated or shown in Table 6and plots for respective evaluation parameters were presented in Figure respectively in figure 2 and 3.

In-vitro dissolution studies of Levetiracetam tablets in 6.8 pH Phosphate Buffer solution: Cumulative % Drug release for F1 -F9 at 20min were found to be in the range of 95.5-99.8% as shown in figure 4. Formulation F7 containing 2mg of sodium starch Glycolate, 6mg of Croscarmellose sodium exerted promising dissolution parameter (Wetting time=89.2±1.2sec, Disintegrating time=1.29±0.89 sec,). Results for Kinetic parameters were presented in Table 7. The final best Formulation F7 is compared with conventional tablet made in house of 125 mg tablets of Levetiracetam and Comparative Dissolution profiles shown in Figure 5.The study reveals thatfast dissolving Levetiracetam tablet F7 shows faster drug release as compared to conventional tablet.Different mathematical models were employed to predict the release mechanisms and compare the release profiles. Linear regression analysis of the mathematical models was employed for the release data of formulation. The correlation coefficients (R2) values showed that the release of drug from formulations best-fitted to Higuchi's

kinetics where it showed the highest (R2) values as shown in table 7and figure 6. The results point to fast release characteristics with a dissolution pattern of drug release, the highest concentration of disintegrant were shown faster dissolution and lowest concentration shown slower dissolution

CONCLUSION: Many conventional solid oral dosage forms are available which releases the drug instantly to obtained fast and complete systemic drug absorption. Dysphasia is a common problem associated with the tablets and capsule which results in high degree of noncompliance. The aim of present study was formulation and in-vitro evaluation of fast dissolving tablets ofLevetiracetam by using direct compression technique. Various parameters like pre & post compressional parameters were tested and final formula was selected based on disintegration time and in-vitro dissolution profile. Evaluation parameters like hardness, friability, weight variation and drug content indicate that values were within permissible limit for all formulations. Disintegration time for all the formulations were found to be in the range of 48-110 sec seconds. The friability was less than 1%. The wetting time and disintegration time were practically good for all formulations results reveals that quantities of Superdisintegrants 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. The results showed that with increasing the concentration of superdisintegrants the disintegration time decreases and the release of the drug increases. On the basis of evaluation parameters, the optimized formulation F7 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.

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