



## RESEARCH ARTICLE

# FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF ANTIEPILEPTIC DRUG

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### Abstract

**Objective:** The objective of the present study was to prepare and evaluate the mouth dissolving tablet of lacosamide using super disintegrants like Guar Gum, and other excipients like microcrystalline cellulose and mannitol in different concentrations by direct compression method. Lacosamide has been shown to be an effective antiepileptic agent appropriate for epilepsy patients.

**Methods:** The mouth dissolving tablets were prepared by a single punch machine using a powder blend of super disintegrants and lacosamide. Post-compression parameters like hardness, weight variation, friability, *in-vitro* dispersion, drug content uniformity, and *in-vitro* drug release studies were carried out for all formulations.

**Results:** All formulations results were within official limits. Fast disintegration time obtained between 35sec. and 128 sec, was within the official limit. Different drug release kinetic models were applied for selecting batches for stability studies.

**Conclusion:** By the *in-vitro* disintegration, it is concluded that formulation prepared by Guar Gum (10%) showed faster disintegration time than that of MCC. This indicates that the use of super disintegrants increases the release of drug from the formulation. Therefore, it can be concluded that such mouth dissolving tablets are suitable delivery systems for lacosamide.

**Keywords:** Bioavailability, epilepsy, fast dissolving tablet, lacosamide, pre-compression parameters.

## INTRODUCTION

Epilepsy is one of the most common central nervous system (neurological) disorders, resulting from stages of abnormal, excessive generation of neuronal disturbances in the brain. Epilepsy is a brain disorder that is identified by chronic epileptic seizures. Epileptic seizures result from the sudden repetitive occurrence of sensory disturbance, causing loss of consciousness, or convulsions, associated with abnormal electrical activity in the brain. About 90% of epilepsy patients are found in developing countries<sup>1</sup>. There are defined causes of epilepsy that are common in paediatrics and geriatrics. In the neonatal period and early infancy, the most common causes are hypoxic-ischemic encephalopathy, CNS infections, trauma, congenital CNS abnormalities, and metabolic disorder. In late infancy and early childhood, the most common febrile seizures may be caused by CNS infections and trauma<sup>2</sup>. Seizures are paroxysmal manifestations of the cerebral cortex. They occur when a sudden imbalance occurs between the excitatory and inhibitory forces within the network of cortical neurons. Cell membrane instability or its physiological changes in its adjacent supporting

cells represent the main pathophysiology of seizures<sup>3</sup>. The fast-dissolving tablets release the medicament in the mouth for absorption through local oro-mucosal tissue and through pre-gastric (oral cavity, pharynx and oesophagus), gastric (stomach) and post-gastric (small and large intestine) segments of the Gastro-Intestinal Tract. Fast dissolving tablets dosage forms are particularly suitable for patients, who have difficulty to swallow traditional tablets with a glass of water<sup>4</sup>. Lacosamide, is a functionalized amino acid with a novel anticonvulsant activity. It is used as antiepileptic drug for partial-onset seizures. Lacosamide has a half life of about 12–16 hrs, Lacosamide is excreted renally, with 95% of the drug eliminated in the urine<sup>5</sup>. The objective of this study was to improve the rapid onset of action of the drug and to provide immediate therapy to the patients. To achieve it fast dissolving tablets of Lacosamide were developed using super- disintegrating agents like Guar gum, MCC. Furthermore this drug delivery system can consumer acceptance by virtue of rapid disintegration, self administration without water or chewing and suitable for the patient having difficulty in swallowing.

## MATERIALS AND METHODS

Lacosamide was obtained gift sample from Dr. Reddy's Laboratories, Hyderabad, India and all other excipients used in this study obtained from pharmaceutical and chemical grade commercial sources.

### Formulation of Lacosamide fast dissolving tablets

Tablets containing Lacosamide were formulated using various super disintegrants like Guar gum, MCC in concentrations ranging from 5-10%. The tablets were prepared by direct compression method. All the ingredients were passed through a sieve number 40 prior to mixing. Lacosamide, Microcrystalline Cellulose, Aspartame and the super disintegrants were properly mixed for 30 min in a suitable container to obtain a uniform blend. The blend was further lubricated with magnesium stearate and talc for 5 min<sup>3</sup>.

### Evaluation of Pre-Compression Parameters:

#### Bulk Density

It is the ratio of the total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder, and the initial volume was noted. This initial volume is called bulk volume.

#### Tapped Density

Weighed quantity of powder blend was taken into a graduated cylinder. The volume occupied by the drug was noted down. Then the cylinder was subjected to 100 taps in density tester (Electro lab), and the volume was measured<sup>6</sup>.

#### The angle of Repose ( $\theta$ ):

A glass funnel is held in place with a clamp on ring support over a tile. Approximately 100 g of powder is transferred into funnel through a mesh size no. 20 keeping the orifice of the funnel blocked by the thumb. When the powder is emptied from the funnel, the angle of the heap to the horizontal plane is measured with a scale. **Carr's Index:**

The compressibility index of the powder blend was determined by Carr's compressibility index. It depends upon the bulk density and tapped density of powder and evaluates the rate at which it packed down<sup>7</sup>. The following formula was used for the determination of Carr's index:

$$\text{Carr's index} = 100 \times \frac{DT - DB}{DT}$$

Where, DT=Tapped density, DB=Bulk density

#### Hausner's Ratio:

It is defined as the ratio of the tapped density to bulk density. It can be calculated by using the formula:

$$\text{Hausner ratio} = \frac{DT}{DB}$$

**Table 1: Composition of lacosamide fast dissolving tablets.**

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Lacosamide (mg)	100	100	100	100	100	100	100	100
Guar gum (mg)	6	12	18	24	-	-	-	-
Sodium Starch Glycolate (mg)	-	-	-	-	6	12	18	24
Micro crystalline cellulose (mg)	83	77	71	65	83	77	71	65
Aspartame (mg)	5	5	5	5	5	5	5	5
Talc (mg)	3	3	3	3	3	3	3	3
Magnesium Stearate (mg)	3	3	3	3	3	3	3	3

**Table 2: Evaluation of flow properties of formulations F1-F8.**

Batch Code	Bulk density (g/ml)±SD*	Tapped density (g/ml)±SD*	Angle of repose ( $\theta$ )±SD*	Carr's index (%)±SD*	Hausner's ratio±SD*
F1	0.36±0.02	0.42±0.02	28.40±0.23	15.66±0.24	1.16±0.01
F2	0.34±0.01	0.41±0.01	24.53±0.21	12.56±0.01	1.12±0.05
F3	0.39±0.14	0.45±0.04	26.51±0.25	13.35±0.18	1.16±0.04
F4	0.37±0.17	0.46±0.03	25.7±0.17	15.58±0.12	1.17±0.06
F5	0.35±0.13	0.38±0.03	28.26±0.19	14.89±0.21	1.15±0.01
F6	0.36±0.15	0.43±0.05	26.24±0.21	13.52±0.01	1.13±0.03
F7	0.37±0.17	0.41±0.01	24.53±0.21	13.35±0.18	1.15±0.01
F8	0.34±0.01	0.41±0.01	24.33±0.21	12.56±0.01	1.12±0.05

N=3, p value: ≤ 0.05

### Evaluation of Post-compression Parameters:

#### Thickness:

The thickness of tablets was measured using Vernier callipers. Tablets are taken and are placed between the two upper jaws and thickness is measured as a replicate of three sets. After adjusting the callipers to zero reading the negative or positive correction values is noted, and the values are estimated<sup>8</sup>.

#### Hardness:

Tablet hardness (tablet crushing strength), the force required for breaking a tablet in a diametric compression of five tablets was measured using Monsanto hardness tester<sup>9</sup>.

#### Friability

Friability test from each batch were examined using Roche friabilator (Electro lab) and the equipment was run for 4 min at 25 revolutions per min. The tablets were taken out, deducted and reweighed, and % friability was calculated<sup>10</sup>.

$$F = \frac{Wt\ initial - Wt\ final}{Wt\ initial} \times 100$$

#### Weight Variation

Weigh individually 20 units selected at random and calculate the average weight. Not more than two the individual weight deviates from the average weight by

more than percentage, and none deviates by more than twice that percentage<sup>11</sup>.

#### Wetting Time

A piece of tissue paper (10.75×12 mm) folded twice was placed in a culture dish (d=6.5 c) containing 6 ml of simulated saliva (phosphate buffer pH 6.8). A tablet was carefully placed on the surface of tissue paper and the time required for simulated saliva to reach the upper surface of the tablet was noted as the wetting time<sup>12</sup>.

#### Water Absorption Ratio

A piece of tissue paper (10.75×12 mm) folded twice was placed in a culture dish (d =6.5 c) containing 6 ml of simulated saliva (phosphate buffer pH 6.8). A tablet was placed on the surface of tissue paper. Initially, the tablet weight was noted before placing in a Petridis. After complete wetting, the wetted tablet was then weighed. The water absorption ratio, r, was determined using equation<sup>13</sup>.

$$r = 100 \times \frac{W_a - W_b}{W_b}$$

Where,  $W_a$ = weight of the tablet after water absorption  
 $W_b$ =weight of the tablet before absorption.

#### In-vitro Disintegration Studies

The test was carried out on 6 tablets using digital tablet disintegration tester (Electro lab). Distilled water at 37±2°C was used as a disintegration media and the time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds<sup>14</sup>.

#### Drug Content

Tablets were selected randomly, and the average weight was calculated. Tablets were crushed in a motor and accurately weighed the amount of tablet powder was taken from the crushed blend. Then the samples were transferred to 100 ml volumetric flask and diluted with 0.1N HCl. The contents were shaken periodically and kept for 2 h for solvation of drug completely. The mixture was filtered in Whatmann filter paper and absorbance was measured at 215 nm using 0.1N HCl as blank<sup>15</sup>.

#### In-vitro Release Study

In-vitro dissolution of Lacosamide fast dissolving tablets was determined in apparatus II as per USP employing a rotating paddle at 50 rpm using 900 ml of 0.1N HCl, at 37±0.5°C. Aliquots of dissolution solution (5 ml) were withdrawn at specific intervals of time and analyzed for drug content by measuring the absorbance

at 215 nm. Cumulative percent of Lacosamide released was calculated and plotted against time<sup>16</sup>.

#### Drug Release Kinetics

To investigate the mechanism of drug release from the prepared tablets, the release data were fitted into first-order, zero-order models<sup>17</sup>.

#### Statistical analysis

Experimental results were expressed as mean±SD. Student's *t*-test and one-way analysis of variance (ANOVA) were applied to check significant differences in drug release from different formulations. Differences were considered to be statistically significant at  $p < 0.05$ .

## RESULTS AND DISCUSSION

In present study total 8 formulations of fast dissolving tablets of Lacosamide were prepared by the means of different superdisintegrants by direct compression method. Pre-compression parameters like bulk density, tapped density, Hausner's ratio, Carr's index and angle of repose were performed for all formulations, and the results were reported in Table 2. The angle of repose of all formulations was found to be in the range of 24.330-30.220. The optimized formulation F8 shown an angle of repose 24.330, which indicates that flow property was good. Carr's index of all formulations was found to be in the range of 12.56-15.66%. The optimized formulation F8 shown 12.56%, which ensures that the flow property is good. Hausner's ratio of all formulations was found to be in the range of 1.12-1.17. The optimized formulation F8 showed 1.12; it indicates that flow property was good. The results of post-compression parameters such as disintegration time, wetting time, water absorption ratio %, hardness, average weight, friability, drug content were shown in Table 3 and Table 4. Disintegration ability to prepare the formulations was evaluated in normal purified water. The time taken for formulations to disintegrate was evaluated. F1, F2, F3, F4 formulations containing guar-gum as 2%, 4%, 6% and 8% concentration disintegrated within 98 sec, 85 sec, 73 sec and 57 sec and F5, F6, F7, F8 formulations containing Microcrystalline cellulose powder disintegrated within 62 sec, 54 sec, 46 sec, 25 sec respectively. Microcrystalline cellulose powder containing formulations, *i.e.*, F5-F8 disintegrates faster than formulations F1-F4 containing guar-gum.

**Table 3: Post compression parameters of formulations F1-F8.**

Batch Code	Hardness (kg/cm <sup>2</sup> ) ±SD* (*n=5)	Friability (%)±SD* (*n=10)	Average weight ±SD*(mg) (*n=20)	Drug content ± SD* (*n=10)
F1	3.3±0.02	0.52±0.04	300±0.83	97±0.08
F2	3.3±0.10	0.65±0.01	300±0.99	98±0.03
F3	3.3±0.02	0.54±0.01	300±0.13	98±0.68
F4	3.5±0.02	0.52±0.03	300±0.16	99±0.75
F5	3.3±0.04	0.51±0.01	299±0.74	97±0.05
F6	3.3±0.06	0.51±0.02	299±0.33	98±0.88
F7	3.5±0.10	0.56±0.05	300±0.14	97±0.94
F8	3.5±0.03	0.66±0.03	300±0.28	99±0.03

**Table 4: Disintegration, wetting time and water absorption of formulations F1-F8.**

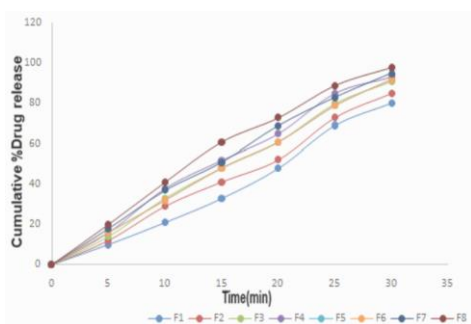
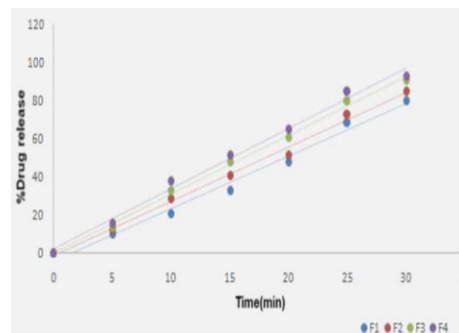
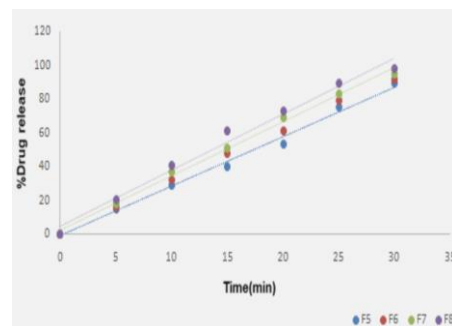
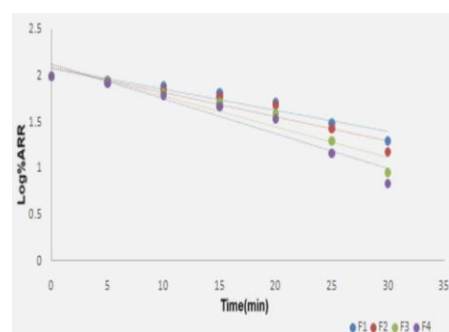
Batch Code	Disintegration time (sec)	Wetting time (sec)	Water absorption ratio %
F1	98	87	52.12±0.66
F2	85	78	59.10±0.28
F3	73	66	63.29±0.45
F4	57	50	70.53±0.10
F5	62	56	56.15±0.35
F6	54	49	63.52±0.10
F7	46	39	66.66±0.24
F8	25	19	80.76±0.20

This may be suggested that an increase in the concentration of super disintegrating agent, faster the disintegration. The reason for the decrease in disintegration time is the ability of microcrystalline cellulose to increase water penetration due to a wicking action which increases tablet porosity and thus lowers disintegration time.

**Table 5: Drug release kinetic studies for all formulations F1-F8.**

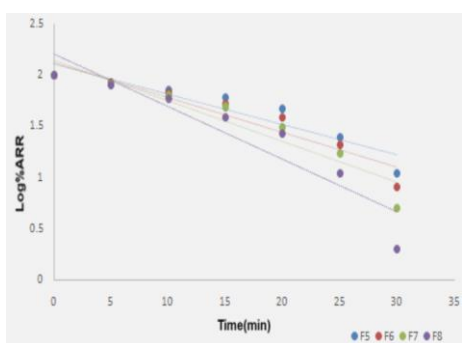
Batch Code	Zero-order R <sup>2</sup> values	First order R <sup>2</sup> values
F1	0.9148	0.9871
F2	0.9163	0.9949
F3	0.9142	0.9971
F4	0.9210	0.9912
F5	0.8779	0.9926
F6	0.8957	0.9921
F7	0.8842	0.9918
F8	0.8651	0.9846

Formulations F1-F4 containing guar-gum has shown the wetting time of 87, 78, 66, 50 sec and formulations F5-F8 containing microcrystalline cellulose powder showed 56, 49, 39, 19 sec respectively. Increase in concentration of disintegrating agent decreases wetting time. Water absorption capacity was found to increase with an increase in the concentration of both guar-gum and microcrystalline cellulose powder. From batches F1-F4 containing guar-gum having more water absorption capacity than F5-F8 containing microcrystalline cellulose powder which could be due to higher water uptake by the natural polymer. The hardness of each batch of tablets was found to be in the range of 3.3-3.5 kg/cm<sup>2</sup>, which ensures good handling characteristics for all formulations. The percentage friability was less than 0.5% for all formulations ensuring that all tablets were mechanically stable and the ranges were found between 0.1-0.6%.

**Figure 1: In-vitro drug release profiles of formulations F1-F8.****Figure 2: Zero order plots of formulations F1-F4.****Figure 3: Zero order plots of formulations F5-F8.****Figure 4: First order plots of formulations F1-F4.**

The entire formulation passed weight variation test as the % weight variation was within the Standard Pharmacopoeia limits. The weights of all the tablets were found to be uniform with low standard deviation values. Drug content was found to be in the range of 97-99.7%. The results indicated that reproducible with minimum batch to batch variability. Formulation F1 containing guar-gum as super-disintegrating agent containing 2% concentration shows 80% drug release at the end of 30 min. The gradual increase in concentration of guar-gum, the formulation F4 containing 8% concentration of guar-gum shows 93% drug release. When compared with formulations F1-F4, formulation F5 contains 2% concentration of F5-F8

containing microcrystalline cellulose powder shown 89% of drug release and gradual increase in the concentration of F5-F8 containing microcrystalline cellulose powder F8 formulation shown 98% of drug release (Figure 4).



**Figure 5: First order plots of formulations F5-F8.**

The drug release data of all formulations were fitted to kinetic models. The results were shown in Table 5 and Figure 2 to Figure 5.  $R^2$  values of First order (0.9846) for formulation (F8) was greater than  $R^2$  values of Zero order (0.8651). Hence, drug release follows First order kinetics.

## CONCLUSIONS

The fast dissolving tablets of Lacosamide were prepared successfully by using a direct compression method. On the basis of different parameters formulation F8 can be considered as a promising formulation. Thus; the objective of this study was achieved. Thus, the “patient-friendly dosage form” especially for paediatrics, geriatrics, bedridden and non-cooperative patients, can be successfully formulated using this technology, providing faster and better drug release, thereby, improving the bioavailability of drug compared to conventional marketed formulations.

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## AUTHOR'S CONTRIBUTION

**Akhtar MS:** Writing original draft, review, methodology, data curation, literature survey, editing.

## DATA AVAILABILITY

Data will be made available on request.

## CONFLICT OF INTEREST

No conflict of interest associated with this work.

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