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. These showed that there was no significant change in residual drug content in mouth dissolving tablets.

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.

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. 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.

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. 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.

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.

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:

Weighted 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.

Compression Parameters:

Hausner's ratio:

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

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

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.

Hardness:

Tablet hardness (tablet crushing strength), the force required for breaking a tablet in a diamic compression of five tablets was measured using Monsanto hardness tester.

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 reweighted, and % friability was calculated:

\[ F = \frac{\text{Wt initial} - \text{Wt final}}{\text{Wt initial}} \times 100 \]

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.10

Wetting Time:
A piece of tissue paper (10.75×12 mm) folded twice was placed in a culture dish (d = 6.5 cm) 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.12

Water Absorption Ratio:
A piece of tissue paper (10.75×12 mm) folded twice was placed in a culture dish (d = 6.5 cm) 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:

\[ r = 100 \times \frac{W_a - W_b}{W_b} \]

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.14

**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.15

**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. The volume withdrawn at each time interval was replaced with a fresh volume of dissolution medium. Cumulative percent of Lacosamide released was calculated and plotted against time.16

**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.17

**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.

### Table 3: Post compression parameters of formulations F1-F8

<table>
<thead>
<tr>
<th>Batch Code</th>
<th>Hardness (kg/cm²) ±SD*</th>
<th>Friability (%) ±SD* (n=10)</th>
<th>Average weight ±SD*(mg) (n=20)</th>
<th>Drug content ±SD* (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>3.3±0.02</td>
<td>0.52±0.04</td>
<td>300±0.83</td>
<td>97±0.08</td>
</tr>
<tr>
<td>F2</td>
<td>3.3±0.10</td>
<td>0.65±0.01</td>
<td>300±0.99</td>
<td>98±0.03</td>
</tr>
<tr>
<td>F3</td>
<td>3.3±0.02</td>
<td>0.54±0.01</td>
<td>300±0.13</td>
<td>98±0.08</td>
</tr>
<tr>
<td>F4</td>
<td>3.5±0.02</td>
<td>0.52±0.03</td>
<td>300±0.16</td>
<td>99±0.75</td>
</tr>
<tr>
<td>F5</td>
<td>3.3±0.04</td>
<td>0.51±0.01</td>
<td>299±0.74</td>
<td>97±0.05</td>
</tr>
<tr>
<td>F6</td>
<td>3.3±0.06</td>
<td>0.51±0.02</td>
<td>299±0.33</td>
<td>98±0.08</td>
</tr>
<tr>
<td>F7</td>
<td>3.5±0.10</td>
<td>0.56±0.05</td>
<td>300±0.14</td>
<td>97±0.94</td>
</tr>
<tr>
<td>F8</td>
<td>3.5±0.03</td>
<td>0.66±0.05</td>
<td>300±0.28</td>
<td>99±0.03</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Batch Code</th>
<th>Disintegration time (sec)</th>
<th>Wetting time (sec)</th>
<th>Water absorption ratio %</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>98</td>
<td>87</td>
<td>52.12±0.66</td>
</tr>
<tr>
<td>F2</td>
<td>85</td>
<td>78</td>
<td>59.10±0.28</td>
</tr>
<tr>
<td>F3</td>
<td>73</td>
<td>66</td>
<td>63.29±0.45</td>
</tr>
<tr>
<td>F4</td>
<td>57</td>
<td>50</td>
<td>70.53±0.10</td>
</tr>
<tr>
<td>F5</td>
<td>62</td>
<td>56</td>
<td>56.15±0.35</td>
</tr>
<tr>
<td>F6</td>
<td>54</td>
<td>49</td>
<td>63.52±0.10</td>
</tr>
<tr>
<td>F7</td>
<td>46</td>
<td>39</td>
<td>66.66±0.24</td>
</tr>
<tr>
<td>F8</td>
<td>25</td>
<td>19</td>
<td>80.76±0.20</td>
</tr>
</tbody>
</table>
Table 5: Drug release kinetic studies for all formulations F1-F8

<table>
<thead>
<tr>
<th>Batch Code</th>
<th>Zero order R² values</th>
<th>First order R² values</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.9148</td>
<td>0.9871</td>
</tr>
<tr>
<td>F2</td>
<td>0.9163</td>
<td>0.9949</td>
</tr>
<tr>
<td>F3</td>
<td>0.9142</td>
<td>0.9971</td>
</tr>
<tr>
<td>F4</td>
<td>0.9210</td>
<td>0.9912</td>
</tr>
<tr>
<td>F5</td>
<td>0.8779</td>
<td>0.9926</td>
</tr>
<tr>
<td>F6</td>
<td>0.8957</td>
<td>0.9921</td>
</tr>
<tr>
<td>F7</td>
<td>0.8842</td>
<td>0.9918</td>
</tr>
<tr>
<td>F8</td>
<td>0.8651</td>
<td>0.9846</td>
</tr>
</tbody>
</table>

Carr’s index of all formulations was found to be in the range of 12.56-15.66%. The optimized formulation F8 showed 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. 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. 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/cm², 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%. 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.

The prepared tablets were evaluated for drug content, and the 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 containing 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 and the results were shown in 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. R² values of First order (0.9846) for formulation (F8) was greater than R² values of Zero order (0.8651). Hence, drug release follows First order kinetics.

CONCLUSION
The fast dissolving tablets of Lacosamide were prepared successfully by using a direct compression method. The in-vitro drug release studies showed that the formulation F8 containing 8% w/w of microcrystalline cellulose powder showed 98% of drug release at the end of 30 min, and formulation F4 which containing 8% w/w of guar-gum showed 93% of drug release at the end of 30 min. Hence, 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.

COMPETING INTERESTS
The authors declare that they have no competing interests.

AUTHOR’S CONTRIBUTION
The manuscript was carried out, written, and approved in collaboration with all authors.

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