FORMULATION AND DEVELOPMENT OF LAMOTRIGINE FAST DISINTEGRATING TABLET

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ABSTRACT
In present research, fast disintegrating tablets of Lamotrigine (drug used in the treatment of epilepsy and bipolar disorder) were prepared using Micro crystalline cellulose and Lactose Monohydrate IP as diluents and Aspartame as sweetening agent along with three different levels of two super disintegrants i.e. sodium starch glycolate and Kyron T-314. The tablets were evaluated for weight variation, hardness, friability, thickness, wetting time, disintegration time (DT) and dissolution study. Optimized batch F3 prepared using concentration of Kyron and Sodium starch glycolate 4% and 2% respectively was showing rapid disintegration of Lamotrigine tablets (15 ± 0.12 sec). Other evaluation parameters of tablets i.e. hardness (3.4 ± 0.17 Kg/cm²), Friability (0.91 ± 0.08%), Weight variation (1.8 ± 0.17 mg) were also found within the standard range for F3 batch tablets. Keywords: Lamotrigine, Super disintegrating agent, bipolar disorder, Lennox-Gastaut syndrome.

INTRODUCTION
Many patients especially children and elderly have difficulty in swallowing tablets and capsules and consequently unable to take medicine as prescribed. Almost 50% of the population is affected by such problem, resulting in the high incidence of non compliance and ineffective therapy[1]. Most pharmaceutical forms for oral administration are formulated for direct ingestion, or for chewing, or for prior dispersion and/or dissolution in water; some of them are absorbed in the mouth (sublingual or buccal tablets). To obviate the problems associated with conventional dosage forms, orally fast disintegrating tablets have been developed, which combine hardness, dosage uniformity, stability and other parameters, with extremely easy administration, since no water is
required for swallowing the tablets and they are thus suitable for geriatric, pediatric and traveling patients\textsuperscript{[2]}.

Fast disintegrating tablets (FDTs) have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industry. Upon introduction into the mouth, these tablets dissolve or disintegrate in the mouth in the absence of additional water for easy administration of active pharmaceutical ingredients. FDTs reduce the time require to disintegrate the tablets and by this way these tablets reduces the onset time\textsuperscript{[3-10]}.

Lamotrigine is an anti epileptic drug and it is approved in the US for the treatment of partial seizures and bipolar disease. Chemically it is $6-(2,3$-dichlorophenyl)-1,2,4-triazine-3,5-diamine. Lamotrigine inhibits sodium currents by selectively binding to the inactivated state of the sodium channel and subsequently suppresses the release of the excitatory amino acid, glutamate\textsuperscript{[11]}.

In present study an attempt has been made to prepare the tablets with minimum disintegration time which finally reduce the time for the onset of action of drug. Tablets were prepared with the two disintegrating agents and their concentrations were optimized.

**MATERIALS AND METHODS**

Materials used in this study were obtained from the different sources. Gift sample of Lamotrigine was obtained from TPL, Ahmedabad, India, Sodium steryl fumarate and Aerosil were gifted from S.D. Fine Chem. Ltd., Mumbai, Super disintegrating agent Sodium Starch Glycolate and Kyron T-314 were obtained from DMV-Fonterra Excipients, Gernamy and Corel Pharma Ltd respectively. Lactose Monohydrate IP was gifted from Signet chemical corporation Pvt. Ltd, Mumbai.

**Preparation of Lamotrigine Fast Disintegrating Tablets:**

All of the formulation components other than the lubricant and glidant were accurately weighed passed through a 40-mesh sieve and mixed in a V-blender for 15 min. The obtained blend was lubricated with sodium stearyl fumarate and Aerosil\textsuperscript{®} for another 5 min and the resultant mixture was directly compressed into tablets. The amount of all the tablet components other than superdisintegrants (Kyron & SSG), lactose &
MCC (filler) were kept constant. Round biconvex tablets of 140 mg in weight were prepared on Rimek rotary tabletting machine.

**Experimental Design:**

Experimental design utilized in present investigation for the optimization of super disintegrants concentration. Concentration of Kyron T-314 was taken as an X1 and concentration of Sodium starch glycolate was taken as an X2. Experimental design was given in the Table 1. Three levels were selected and coded as -1= 2%, 0=3%, +1=4%. Formulas for all the experimental batches were given in Table 2

**TABLE 1: EXPERIMENTAL DESIGN LAYOUT**

<table>
<thead>
<tr>
<th>Batch code</th>
<th>X1</th>
<th>X2</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>F2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>F3</td>
<td>1</td>
<td>-1</td>
</tr>
<tr>
<td>F4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>F5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>F6</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>F7</td>
<td>-1</td>
<td>1</td>
</tr>
<tr>
<td>F8</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>F9</td>
<td>-1</td>
<td>-1</td>
</tr>
</tbody>
</table>

X1 = Concentration of Kyron  
X2 = Concentration of Sodium Starch Glycolates

**TABLE 2: FORMULA AS PER EXPERIMENTAL DESIGN**

<table>
<thead>
<tr>
<th>Batches</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRUG</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>LACTOSE</td>
<td>95.1</td>
<td>96.5</td>
<td>97.9</td>
<td>96.5</td>
<td>97.9</td>
<td>99.3</td>
<td>97.9</td>
<td>99.3</td>
<td>100.7</td>
</tr>
<tr>
<td>MCC</td>
<td>24.5</td>
<td>24.5</td>
<td>24.5</td>
<td>24.5</td>
<td>24.5</td>
<td>24.5</td>
<td>24.5</td>
<td>24.5</td>
<td>24.5</td>
</tr>
<tr>
<td>KYRON</td>
<td>5.6</td>
<td>5.6</td>
<td>5.6</td>
<td>4.2</td>
<td>4.2</td>
<td>4.2</td>
<td>2.8</td>
<td>2.8</td>
<td>2.8</td>
</tr>
<tr>
<td>SSG</td>
<td>5.6</td>
<td>4.2</td>
<td>2.8</td>
<td>5.6</td>
<td>4.2</td>
<td>2.8</td>
<td>5.6</td>
<td>4.2</td>
<td>2.8</td>
</tr>
<tr>
<td>ASPARTAME</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>AEROSIL</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>SSF</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>TOTAL</td>
<td>140</td>
<td>140</td>
<td>140</td>
<td>140</td>
<td>140</td>
<td>140</td>
<td>140</td>
<td>140</td>
<td>140</td>
</tr>
</tbody>
</table>

All the weights are in milligrams.
Evaluation parameters:

Uniformity of weight

Randomly selected 20 tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation was calculated. IP limit for weight variation in case of tablets weighting up to 120 mg is ± 10%, 120 mg to 300 mg is ± 7.5% and more than 300 mg is ± 5%. The weights were determined to within ±7.5% by using Sartorius balance (Model CP- 224 S)\(^{[15]}\).

Tablet hardness

The hardness of the tablets was determined by diametral compression using a dial type hardness tester (Model no 1101, Shivani Scientific Ind). A tablet hardness of about 2-4 kg/cm\(^2\) is considered adequate for mechanical stability\(^{[16]}\).

Tablet friability

The friability of the tablets was measured in a Roche Friabilator (Campbell Electronics, Mumbai). Tablets of a known weight (\(W_0\)) or a sample of 20 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (\(W\)) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %\(^{[17]}\).

\[
\text{% Friability} = \frac{W_0 - W}{W_0} \times 100
\]  

(1)

In-vitro disintegration test

The test was carried out on 6 tablets using Tablet disintegration tester ED-20 (Electro lab, Mumbai, India). Distilled water at 37ºC ± 2ºC was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds\(^{[18]}\).

Tablet thickness

Tablet thickness was measured very simply. Tablets were taken and their thickness was measured using Vanier calipers. The thickness was measured by placing tablet between two arms of the Vanier calipers\(^{[19]}\).

In-vitro dissolution profile of prepared Lamotrigine FDT.

The release rate Lamotrigine from fast dissolving tablets was determined using Indian pharmacopoeia dissolution testing apparatus I (paddle method). The dissolution
test was performed using 900 ml of 0.1 N HCl (pH=1.2), at 37 ±0.5°C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at 1, 3, 5, 10, 15, 20 and 30min. The samples were replaced with fresh dissolution medium of same quantity. The samples were filtered through whatman filter paper. Absorbance of these solutions was measured at 254 nm using a Shimadzu UV-1601 UV/Visible double beam spectrophotometer. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve\[20-22\].

RESULTS AND DISCUSSION:

Fast dissolving tablets were prepared for to minimize disintegration time and hence getting rapid action of drug. In present work concentration of Kyron T314 and Concentration of Sodium starch glycolate were selected as X1 and X2 respectively. Prepared tablets were evaluated for different evaluation parameters.

Uniformity of weight

Weight variation test for tablets was carried out for 20 tablets. Standard for weight variation test were given in the Indian pharmacopoeia. All the evaluated tablets were found in the standard range of weight, ±7.5%. Hence FDT of Lamotrigine passes the test for weight variation.

Tablet hardness

The hardness of the tablets was determined by diametral compression using a dial type hardness tester (Model no 1101, Shivani Scientific Ind). A tablet hardness of about 2-4 kg/cm\(^2\) is considered adequate for mechanical stability. Results of hardness testing are shown in Table 3. All the tablets were passed the hardness test.

Tablet disintegration test

Disintegration test was carried out on 6 tablets using Tablet disintegration tester ED-20 (Electro lab, Mumbai, India) distilled water at 37°C ± 2°C was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds. Results are shown in table 3.

Disintegration time of batch F3 was smaller as compared to the other batches. Large concentration of sodium starch glycolate was producing sticky mass which was
retained on the sieve of disintegrating test apparatus so finally it causes the higher disintegration time.

**TABLE 3: RESULTS OF VARIOUS EVALUATION PARAMETERS**

<table>
<thead>
<tr>
<th>Batch no.</th>
<th>Weight variation (mg)</th>
<th>Hardness (Kg/cm²)</th>
<th>Disintegration time (sec)</th>
<th>Friability (%w/w)</th>
<th>Behaviour of tablets under observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>1.6 ± 0.21</td>
<td>3.25 ± 0.20</td>
<td>22 ± 0.22</td>
<td>0.91 ± 0.12</td>
<td>Soft mass retain in 10 # sieve</td>
</tr>
<tr>
<td>F2</td>
<td>2.7 ± 0.19</td>
<td>3.3 ± 0.13</td>
<td>20 ± 0.21</td>
<td>0.78 ± 0.16</td>
<td>Soft mass retain in 10 # sieve</td>
</tr>
<tr>
<td>F3</td>
<td>1.8 ± 0.17</td>
<td>3.4 ± 0.17</td>
<td>15 ± 0.12</td>
<td>0.91 ± 0.08</td>
<td>No mass retain</td>
</tr>
<tr>
<td>F4</td>
<td>3.4 ± 0.10</td>
<td>3.22 ± 0.17</td>
<td>25.5 ± 0.14</td>
<td>0.89 ± 0.18</td>
<td>Soft mass retain in 10 # sieve</td>
</tr>
<tr>
<td>F5</td>
<td>2.9 ± 0.14</td>
<td>3.45 ± 0.12</td>
<td>29.75 ± 0.36</td>
<td>0.94 ± 0.22</td>
<td>Soft mass retain in 10 # sieve</td>
</tr>
<tr>
<td>F6</td>
<td>2.9 ± 0.23</td>
<td>3.5 ± 0.15</td>
<td>31 ± 0.14</td>
<td>0.95 ± 0.26</td>
<td>Hard mass retain in 10 # sieve</td>
</tr>
<tr>
<td>F7</td>
<td>2.5 ± 0.24</td>
<td>3.31 ± 0.12</td>
<td>26 ± 0.09</td>
<td>0.89 ± 0.25</td>
<td>Soft mass retain in 10 # sieve</td>
</tr>
<tr>
<td>F8</td>
<td>2.7 ± 0.13</td>
<td>3.44 ± 0.21</td>
<td>33 ± 0.27</td>
<td>0.96 ± 0.13</td>
<td>Soft mass retain in 10 # sieve</td>
</tr>
<tr>
<td>F9</td>
<td>2.6 ± 0.18</td>
<td>3.6 ± 0.13</td>
<td>38 ± 0.29</td>
<td>0.84 ± 0.14</td>
<td>Hard mass retain in 10 # sieve</td>
</tr>
</tbody>
</table>

**Tablet friability**

The friability of the tablets was measured in a Roche Friabilator (Camp-bell Electronics, Mumbai). Tablets of a known weight (W₀) or a sample of 20 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated. The weight loss should not be more than 1 %. Results were shown in table. All the batches were passed the test for friability.

**In-vitro dissolution profile of prepared Lamotrigine FDT**

The release rate Lamotrigine from fast dissolving tablets was determined using Indian pharmacopoeia dissolution testing apparatus I (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl (pH=1.2), at 37 ±0.5°C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at 1, 3, 5, 10, 15, 20 and 30min. Results of dissolution profile were shown in table and the comparison of dissolution profile was given in figure 1. Batch F3 was showing better drug release as compared to other batches.
CONCLUSION

Fast disintegrating tablets can be used to minimize the onset of action of drug. Rapid disintegration can achieved using super disintegrating agents. The results of above performed experiments revealed that the concentration of super disintegrating agents, sodium starch glycolate and Kyron T 314 significantly affect the disintegration time of prepared tablets. Batch F3 was showing rapid disintegration (15 ±.012 sec) among all the prepared batches. Optimized concentrations of Kyron T-314 and SSG were 4% and 2% respectively which was showing rapid disintegration of Lamotrigine tablets and helps to get immediate action of Lamotrigine.

REFERENCES


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