Formulation and Evaluation of Lamotrigine Spherules with Robust Gelation Technique

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ABSTRACT:
Many freshly created high-potential medications have low water solubility, which is a challenge in formulation development. The study aimed to improve the solubility of Lamotrigine, a weakly soluble medication classified as BCS class II, by solid dispersion techniques. Lamotrigine solid dispersion was created using the solvent evaporation method, and the formulation was assessed using stability tests, Fourier transform infrared spectroscopy (FTIR), and physical properties. Preformulation investigations yielded satisfactory results, therefore pellets were formed and evaluated. Solid dispersion had a different pharmacokinetic profile than pure medication, which could be attributable to Lamotrigine's faster dissolution rate from solid dispersion.

Solid dispersions have sparked widespread interest as an effective technique of increasing the dissolution rate and thus bioavailability of a variety of weakly water-soluble medicines. Solid dispersions of weakly water-soluble medicines with water-soluble carriers have reduced the occurrence of these difficulties and increased solubility.

INTRODUCTION:
Poorly water-soluble medications are becoming increasingly problematic in terms of achieving sufficient dissolving within the gastrointestinal tract, which is required for good bioavailability. It is the challenge of medicinal chemists to ensure that new medications are not only pharmacologically active but also have enough solubility to enable fast enough dissolution at the site of delivery, which is commonly the gastrointestinal system. It is estimated that 40% or more of new chemical entities (NCEs) being identified through combinatorial screening programs are poorly soluble in water, which is a critical determinant of oral bioavailability and solubility of many newly developed high-potential drugs is an obstacle in formulation development. Furthermore, the Biopharmaceutical Classification System (BCS) highlights dissolution as the rate-limiting step for oral absorption of class II and IV drugs. Solubilization techniques include the addition of a cosolvent, salt formation, prodrug design, complexation, particle size reduction, and the use of surface active agents, the use of solvate and...
hydrates, polymorphs, hydrotrophy, the use of absorbents, pH adjustment, solubilizing vehicles, and so on. Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix during the solid stage to produce higher dissolution rate, sustained release of pharmaceuticals, altered solid state properties, and enhanced release of drugs. Traditionally, solid dispersions (SDs) were employed to increase the dissolving characteristics and bioavailability of weakly water-soluble medicines. Lamotrigine is an antiepileptic medication of BCS class II that creates significant solubility issues. To boost the solubility of the medicine, solid dispersion was used with two polymers HPMC, and the solid dispersion mixture was evaluated, and pellets were made after receiving satisfactory findings. The orifice-ionic gelation technique using sodium alginate and calcium chloride was used to make lamotrigine pellets in this study. Pellets formulated with lamotrigine were tested for particle size, entrapment efficiency, in-vitro drug release, rheology study, and loose crystal surface. [2]

MATERIALS:
1. Lamotrigine drug
2. HPMC
3. Ethanol
4. Sodium alginate solution
5. Calcium chloride
6. Phosphate buffer [pH 6.8, pH 7.4]
7. 0.1N HCL

METHODS:
• Preparation of Solid Dispersion:

![Fig 1: Lamotrigine Solid Dispersion](image)

For the preparation of solid dispersion of Lamotrigine the method used is known as ‘solvent evaporation method’. In this method the required amount of lamotrigine drug is dissolved in required amount of solvent i.e. Ethanol along with polymer i.e. HPMC further the solvent was completely evaporated at 45 degree celcious with contineous stirring to obtain dry mass
• Preparation of Pellets:

For the preparation of pellets of lamotrigine solid dispersion the method used is Orifice ionic gelation technique. In this method the sodium alginate solution was prepared in 50 ml of water and solid dispersion was added to the solution further separately prepare 10 % Calcium chloride solution . To this solution added dispersed solution drop by drop by continuous stirring at less than 300 rpm further they are dried for 2 days at room temperature in Desicator

EVALUATION OF THE LAMOTRIGINE SOLID DISPERSION:

1. physical Appearance:
Colour and appearance were assessed for the two batches of Lamotrigine solid dispersions

2. Lamotrigine content determination:
An accurately weighed amount of each preparation was dissolved in a small volume of methanol and then diluted further with methanol. The amount of lamotrigine was measured spectrophotometrically at 308 nm using Perkin Elmer UV-visible spectrophotometer

3. Stability studies:
Stability tests were performed on pharmacological substances packaged in a container closure system that is identical to or resembles the packing intended for storage and distribution. Stability tests were conducted on both batches of solid dispersion by storing 1 gm of solid dispersions and excipients in an amber screw-capped bottle at room temperature for 4 weeks. After four weeks, the solid dispersions and excipients were visually inspected for any physical changes, and the drug content was estimated

4. Infrared spectroscopy:
The infrared spectra (IR) of Lamotrigine and solid dispersions were obtained using FTIR (Perkin Elmer 1600 Series). The KBr pellet method was used to collect the IR spectra

5. Flow qualities:
The flow properties of solid dispersion were investigated by finding Carr’s index and angle of repose

CHARACTERISTICS OF PELLETS:

1. Determination of Moisture Content:
The Formulations were subjected to Moisture Content Study, by placing the Micropellets at 60°C for 3 hr in an Hot Air Oven[2]

2. **Loose Surface Crystal Study (LSC):**
This study was carried out to determine the amount of drug present on the surface of micropellets, which could be released immediately in the dissolving fluid. 100mg of micropellets (# 22 size) were suspended in 100ml of phosphate buffer (pH 6.8) to simulate the dissolving media. The materials were violently agitated in a mechanical shaker for 15 minutes. The amount of medication leached from the surface was measured spectrophotometrically at 308nm. The percentage of drug released in comparison to the amount of drug enclosed in the sample was recorded[2]

3. **Determination of Drug Entrapment Efficacy:**
About 100mg of micropellets (# 22 sizes) were carefully weighed and dissolved in 25ml of phosphate buffer (pH 7.4) overnight, and an aliquot of the filtrate was spectrophotometrically analysed at 308 nm using Perkin Elmer after adequate dilution. The method’s dependability was determined by doing a recovery analysis using a known dose of drug, with or without polymer. Recovery rates averaged 98.59 ± 0.50%. Each batch’s drug concentration was measured in micropellets of different sizes, and the mean ± SD was calculated. The formula to calculate Drug Entrapment Efficiency (DEE) is as follows[2]

\[
\%\text{DEE} = \frac{\text{Actual Drug Content}}{\text{Theoretical Drug Content}} \times 100
\]

4. **Study of Invitro Dissolution:**
To investigate drug release from the micropellets, the USP Dissolution device I (Electrolab) was utilised. For two batches, the dissolve conditions (100 mg pellets, 37± 2°C, 100 rpm, 1000 ml of USP pH 1.2, n = 3, coefficient of variation < 0.05) were kept constant. A 2 millilitre sample was taken out at predetermined intervals, and after a proper dilution, it was measured at 308 nanometers using a Perkin Elmer spectrophotometer[2]

**RESULTS:**
**EVALUATION OF THE LAMOTRIGINE SOLID DISPERSION:**
1. **Physical Appearance:**

   ![Lamotrigine Solid Dispersion](image)

   Using a solvent evaporation process, fine powder lamotrigine dispersions were created.

2. **Finding the Uniform Lamotrigine Content:**
It was discovered that the produced formulations’ drug content uniformity was 96.54±2.31
3. **Investigations on the stability of two batches of solid dispersions:**

Stability studies were carried out by storing 1gm of solid dispersion and excipient (HPMC) in amber coloured bottles at room temperature for 4 weeks. These batches not showed any significant change.

4. **IR Spectroscopy:**

**TABLE 1: IR Interpretation of Lamotrigine Solid Dispersion**

<table>
<thead>
<tr>
<th>Reported Range Cm⁻¹</th>
<th>Observed Cm⁻¹</th>
<th>Functional Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>3490 - 3430</td>
<td>3451.37</td>
<td>Heterocyclic amine N-H Stretch</td>
</tr>
<tr>
<td>3360 - 3310</td>
<td>3329.84</td>
<td>Aliphatic Secondary Amine, &gt;NH Stretch</td>
</tr>
<tr>
<td>3330 - 3250</td>
<td>3210.64</td>
<td>N-H Stretching Aliphatic Primary Amine</td>
</tr>
<tr>
<td>3000 - 2840</td>
<td>2923.61</td>
<td>C-H Stretching Alkane</td>
</tr>
<tr>
<td>2000 - 1660</td>
<td>1620.29</td>
<td>Aromatic Combination Bands</td>
</tr>
<tr>
<td>1560 - 1540</td>
<td>1556.36</td>
<td>Aliphatic Nitro Compound N-O Stretch</td>
</tr>
<tr>
<td>1555 - 1485</td>
<td>1492.01, 1462.05</td>
<td>C=C-C, Stretch, Aromatic Ring</td>
</tr>
<tr>
<td>1385 - 1380</td>
<td>1384.16</td>
<td>C-H Bend Alkane Geminal dimethyl</td>
</tr>
<tr>
<td>1190 - 1130</td>
<td>1144.35</td>
<td>2° Amine, CN Stretch</td>
</tr>
<tr>
<td>1150 - 1085</td>
<td>1112.33</td>
<td>Aliphatic Ether Stretch</td>
</tr>
<tr>
<td></td>
<td>1055.13</td>
<td></td>
</tr>
<tr>
<td>1225 - 950</td>
<td>950</td>
<td>Aromatic C-H in Plane Bend</td>
</tr>
<tr>
<td>840 - 790</td>
<td>790</td>
<td>C=C Bend Alkene</td>
</tr>
<tr>
<td>850 - 550</td>
<td>717</td>
<td>C-Cl Stretch</td>
</tr>
</tbody>
</table>
5. Flow properties:

**TABLE 2: Evaluation of Flow Properties of Lamotrigine Solid Dispersion**

<table>
<thead>
<tr>
<th>Bulk Density</th>
<th>Tapped Density</th>
<th>Compressibility Index (%)</th>
<th>Hausners Ratio</th>
<th>Angle of Repose (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2857</td>
<td>0.3333</td>
<td>14.28</td>
<td>1.16</td>
<td>26.56</td>
</tr>
</tbody>
</table>

Compressibility Index = Excellent, Hausners Ratio = Good, Angle of Repose = Good

14.28 is the solid dispersions' compressibility index value. This suggests that the powder blend has Excellent flow characteristics. The solid dispersions' angle of repose value of 26.56 were found to be Good in accordance with the flow chart. Because of the good flow feature, compressing the tablet would require less lubricant.

**CHARACTERISTICS OF PELLETS:**

1) Moisture Content:

The all-around efficiency of the optimised drying conditions is indicated by the low moisture content of the pellets. Better medication stability in the pellets is ensured by low moisture content.

**TABLE 3: Evaluation of Moisture Content of Pellets**

<table>
<thead>
<tr>
<th>Batches</th>
<th>Moisture Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch 1</td>
<td>1.42</td>
</tr>
<tr>
<td>Batch 2</td>
<td>1.40</td>
</tr>
</tbody>
</table>

2) Loose Surface Crystal:

One crucial factor that indicated how much medication was present on the pellet surface without adequate trapping was the loose surface crystal (LSC) investigation. Copolymer concentration increased, and LSC as a percentage declined dramatically.
TABLE 4: Loose Surface Crystal Study of Pellets

<table>
<thead>
<tr>
<th>Batches</th>
<th>Loose Surface Crystal Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch 1</td>
<td>3.64 ±0.2</td>
</tr>
<tr>
<td>Batch 2</td>
<td>3.60 ±0.23</td>
</tr>
</tbody>
</table>

3) Drug Entrapment Efficiency:
Table 5 demonstrates that both batches drug entrapment effectiveness was good.

TABLE 5: Evaluation of Drug Entrapment Efficiency of Pellets

<table>
<thead>
<tr>
<th>Batches</th>
<th>Drug Entrapment Efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch 1</td>
<td>97.52±0.30</td>
</tr>
<tr>
<td>Batch 2</td>
<td>97.45±0.25</td>
</tr>
</tbody>
</table>

4) In-Vitro Dissolution Study:
Drug release investigations were conducted in stomach fluid (SGF). Drug release profiles were given by charting the amount of Lamotrigine released over time. Table 6,7 and Figure 9,10 Respectively demonstrate the release test findings for alginate-based pellets. Lamotrigine was released rapidly, with over 90% release within 30 min.

TABLE 6: Dissolution Studies of Batch1 Pellets

<table>
<thead>
<tr>
<th>Time (Hr)</th>
<th>Percentage Drug Release</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>16.20</td>
</tr>
<tr>
<td>10</td>
<td>28.30</td>
</tr>
<tr>
<td>15</td>
<td>44.06</td>
</tr>
<tr>
<td>20</td>
<td>62.66</td>
</tr>
<tr>
<td>30</td>
<td>93.89</td>
</tr>
</tbody>
</table>

![Graph showing total drug release percentage over time](image-url)

**Fig 6: Release Profile of Batch**
TABLE 7: Dissolution Studies of Batch 2 Pellets

<table>
<thead>
<tr>
<th>Time (Hr)</th>
<th>Percentage Drug Release</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>15.23</td>
</tr>
<tr>
<td>10</td>
<td>28.25</td>
</tr>
<tr>
<td>15</td>
<td>43.18</td>
</tr>
<tr>
<td>20</td>
<td>60.02</td>
</tr>
<tr>
<td>30</td>
<td>91.31</td>
</tr>
</tbody>
</table>

Fig 7: Release Profile of Batch 2

Conclusion:
Lamotrigine’s solubility was found to be enhanced by the solid dispersion approach in vitro dissolution experiments, as well as by the combination of polymers. Solid dispersion has superior flow characteristics, making formulation simple. The medication and the excipient did not interact, according to the FTIR and stability experiments. The pellets were prepared using a straightforward, repeatable method called orifice ionotropic gelation, which yields beads with consistent sizes and shapes. The prepared beads were distinct and spherical in shape. Sodium alginate pellets demonstrated a good drug entrapment efficiency, suggesting that the drug was effectively entrapped. Moreover, the LSC data suggested that the drug was less surface-active. In vitro studies suggest that sodium alginate aids in drug release from pellets, with over 90% liberated after 30 minutes.

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