Optimization of carbamazepine-loaded nanoemulsions for nose-to-brain delivery

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Introduction

The intranasal route is a promising alternative for the emergency treatment of epileptic seizures, due to its advantages, such as the possibility of directing the drugs from the nose directly to the brain (nose-to-brain delivery), avoiding the need to cross the blood-brain barrier and increasing the speed of therapeutic action. In this context, lipid-based nanosystems such as nanoemulsions, are promising vehicles to transport anti-epileptic drugs with lipopholic characteristics [1, 2]. Nanoemulsions are colloidal systems typically formed by oil droplets dispersed in water and stabilized by one or two surfactants. They improve drug delivery, particularly lipopholic molecules [3].

Additionally, the nasal administration of drugs with the objective of reaching the brain has been gaining relevance due to the advantages it presents, such as: large surface for the absorption of drugs; easy administration and dose adjustment; non-invasive and painless character; rapid absorption and onset of action of drugs; avoids the effect of first hepatic passage, consequently, nasal doses of drugs are often 2 to 10 times lower than oral doses; between others [4].

Aim

The purpose of this work was to optimize a nanoemulsion for the nose-to-brain delivery of carbamazepine.

Methodology

Lipid-drug solubility tests

The solubility of carbamazepine was tested on four different liquid lipids (oleic acid, vitamin E, Miglyol®812 and Cetiol®W), through the addition of drug (0.05 g; 0.025 g) to the lipid (0.95 g; 0.975 g). The mixture was vigorously stirred, followed by visual observation to check for the presence or absence of drug crystals.

Evaluation of the compatibility between lipids

According to the results of the lipid-drug solubility studies, oleic acid was used to prepare the nanoemulsion and its compatibility with other liquid lipids was evaluated. For this, the following combinations were vigorously stirred: oleic acid + vitamin E, oleic acid + Miglyol®812 and oleic acid + Cetiol®W. Finally, it was verified, by visual observation, the existence or absence of miscibility between the two lipids.

Preparation of nanoemulsions

For the preparation of the nanoemulsions, the lipids were heated at 70°C. In parallel, the aqueous phase (composed by Tween®80 and Poloxamer 188) was heated at the same temperature, added to the former and homogenized under high-speed stirring, using an Ultra-Turrax®, at 13400 rpm during 5 minutes. The emulsion obtained was placed under a probe sonicator, with an amplitude of 70%, during 15 minutes. The nanoemulsion formed was transferred to glass vials and cooled down to room temperature.

Measurement of the droplet sizes

The droplet sizes of the nanoemulsions were measured by Laser Diffractionmetry (LD), using a Mastersizer 3000. Volume distributions of 50 (Dv50) and 90% (Dv90) were measured, referring to the percentage of particles with sizes less than or equal to the specified values [3]. Results are represented as the average of five independent measurements (n = 5) ± standard deviation (SD). To obtain an indication of the particle size distribution span, the span factor was calculated using the following equation:

\[ \text{Span} = \frac{Dv90 - Dv10}{Dv50} \]

Evaluation of the stability of the nanoemulsions

The stability of the prepared nanoemulsions was assessed by measuring the size of the droplets on day 0 and 90 days after storage (5 ± 1°C).

Results

Lipid-drug solubility tests

The absence of drug crystals is a consequence of good drug solubility in the lipids. Thus, and from the results of Table 1, oleic acid was the liquid lipid that presented the best results and, therefore, it was chosen for the preparation of the nanoemulsions.

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Concentration in %</th>
<th>Oil crystals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oleic acid</td>
<td>5,0</td>
<td>-</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>5,0</td>
<td>-</td>
</tr>
<tr>
<td>Miglyol®812</td>
<td>5,0</td>
<td>+</td>
</tr>
<tr>
<td>Cetiol®W</td>
<td>5,0</td>
<td>+</td>
</tr>
</tbody>
</table>

Evaluation of the compatibility between lipids

From Table 2 it can be seen that all the tested lipids showed good compatibility. In this way, the results of the size measurement will support the choice of the two liquid lipids for the preparation of the nanoemulsions, being selected the combination that presents the best droplet sizes.

<table>
<thead>
<tr>
<th>Lipid Lipid</th>
<th>Compatibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oleic acid + Vitamin E</td>
<td>Miscible</td>
</tr>
<tr>
<td>Oleic acid + Miglyol®812</td>
<td>Miscible</td>
</tr>
<tr>
<td>Oleic acid + Cetiol®W</td>
<td>Miscible</td>
</tr>
</tbody>
</table>

Measurement of the droplet sizes

For the nanoemulsion prepared from a combination of oleic acid with Vitamin E, the results obtained indicate that, at the time of preparation, 90% of the droplets (Dv90) had a size equal to or less than 320 ± 0,00 mm and that the average size (Dv50) was 84,9 ± 0,00 nm. The span factor is 1,30.

For the nanoemulsion prepared from the combination of oleic acid with Miglyol®812, the results obtained indicate that, when preparing, 90% of the particles (Dv90) had a size less than or equal to 238 ± 0,00 mm and that average size (Dv50) was 77 ± 0,00 nm. The span factor is 2,77.

Finally, for the nanoemulsion prepared from the combination of oleic acid with Cetiol®W, the results obtained indicate that, when preparing, 90% of the particles (Dv90) had a size less than or equal to 216 ± 0,00 mm and that the average size (Dv50) was 68,7 ± 0,00 nm. The span factor is 2,83.

Therefore, the nanoemulsion that showed the best results was the one that used the combination of oleic acid with Cetiol®W, since smaller droplets were formed.

Evaluation of the stability of the nanoemulsions

By analyzing Table 3 and Table 4, it was found that, after storing the formulations, the following occurred:

- Small decrease in the droplet size of the oleic acid + Vitamin E nanoemulsion (span factor is 3,50), which is not significant;
- Small increase in the droplet size of the oleic acid + Miglyol®812 nanoemulsion, which may be related to the occurrence of aggregation, although this was not visible to the naked eye (span factor is 3,38);
- Minimal variation in the droplet size of the oleic acid + Cetiol®W nanoemulsion, which was considered the most stable formulation (span factor is 2,16).

<table>
<thead>
<tr>
<th>Span factor</th>
<th>Span factor</th>
<th>Span factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>oleic acid + Vitamin E</td>
<td>2,77</td>
<td>2,83</td>
</tr>
<tr>
<td>oleic acid + Miglyol®812</td>
<td>3,38</td>
<td>2,16</td>
</tr>
</tbody>
</table>

Conclusion

Although promising, the stability of the developed nanoemulsions must be confirmed for a longer period, evaluating other characterization parameters, such as the zeta potential and drug encapsulation efficiency. In addition, it will be necessary to optimize the parameters of the production method. In the future, it will also be necessary to evaluate the biocompatibility of the selected nanoemulsion, through cytotoxicity tests in nasal epithelial cells, as well as its ability to permeate these cells, predicting its potential for nose-to-brain delivery.

References