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Abstract
Objective: To evaluate the enhancement of aqueous solubility of a poorly water soluble drug ritonavir by forming its complex with a phospholipid (Phospholipon®90H).

Disciplines
Pharmacy and Pharmaceutical Sciences

Comments

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The enhancement of the aqueous solubility of ritonavir via formulation of a drug-phospholipid complex
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Objective
To evaluate the enhancement of aqueous solubility of a poorly water soluble drug ritonavir by forming its complex with a phospholipid (Phospholipon® 90H).

Methods
The ritonavir-phospholipid complex (RPC) was prepared using a modified solvent evaporation method. A circumscribed central composite design, as shown in table 1, was used to analyze, and optimize the formulation and the process variables to obtain acceptable ritonavir-phospholipid complex (RPC). The influence of phospholipid-to-drug ratio (X1, w:w), reaction temperature (X2, °C) and the reaction time (X3, h) on the entrapment efficiency of ritonavir in RPC were evaluated. The prepared RPC was then characterized by Fourier Transformed Infrared (FTIR) Spectroscopy, Differential Scanning Calorimetry (DSC), Powder X-Ray Diffraction (PXRD), and Scanning Electron Microscopy (SEM). Additionally, the RPC was evaluated for apparent aqueous solubility, and the release of ritonavir in-vitro.

Table 1: Coded levels and “Real” values for each variable studied

<table>
<thead>
<tr>
<th>Factors</th>
<th>Levels</th>
<th>-1.732</th>
<th>-1</th>
<th>0</th>
<th>+1</th>
<th>+1.732</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phospholipid: drug ratio</td>
<td>(X1, w:w)</td>
<td>0.5</td>
<td>1.01</td>
<td>1.75</td>
<td>2.49</td>
<td>3.0</td>
</tr>
<tr>
<td>Reaction temperature</td>
<td>(X2, °C)</td>
<td>40</td>
<td>44.05</td>
<td>50</td>
<td>55.95</td>
<td>60</td>
</tr>
<tr>
<td>Reaction time (X3, h)</td>
<td>(X3, h)</td>
<td>1</td>
<td>1.41</td>
<td>2</td>
<td>2.59</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 2: Apparent aqueous solubility of the samples

<table>
<thead>
<tr>
<th>Sample</th>
<th>Aqueous solubility (µg/ml)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritonavir</td>
<td>0.41 ± 0.04</td>
</tr>
<tr>
<td>Physical Mixture</td>
<td>2.09 ± 0.35</td>
</tr>
<tr>
<td>RPC</td>
<td>15.73 ± 0.59</td>
</tr>
</tbody>
</table>

* Data expressed as mean ± Std. Dev. n = 3

Results (contd.)

The apparent aqueous solubility of ritonavir, the physical mixture of ritonavir with Phospholipon® 90H, and the RPC are shown in table 2.

The results showed that formulation of RPC significantly increased the aqueous solubility of ritonavir. Additionally, the in-vitro dissolution results showed that, at the end of 10 hours, free ritonavir showed 32.47% release; whereas, the drug release from RPC was 99.61%.

This increase in the solubility and the dissolution characteristics of the complex may be explained by the amphiphilic nature of the complex, as well as possible amorphization of the drug by the phospholipid.

Conclusions
The prepared RPC showed a significant (~30-fold) enhancement in the apparent aqueous solubility, as well as the dissolution behavior of ritonavir. Drug-phospholipid complexes can serve as potential alternative strategy for enhancing the aqueous solubility of poorly water soluble drugs such as ritonavir.